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American Heart Journal

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Original Communications

AN ANGIOPULMOGRAPHIC STUDY OF THE LESSER CIRCULATION IN MITRAL STENOSIS

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SINCE 1949 angiocardiography has been used in our institution not only as a useful diagnostic tool for the diagnosis of congenital heart diseases, but also as a valuable method for the evaluation of patients undergoing mitral commissurotomy.

In a previous study we have described the angiocardiographic features of the heart in mitral stenosis and in mitral insufficiency.[1] This report deals with the angiopulmographic aspects of the lesser circulation in patients with mitral stenosis. A correlation will also be made between the angiopulmographic picture of the pulmonary vascular tree in patients with mitral stenosis and some clinical and hemodynamic data.

MATERIAL AND METHODS

Angiocardiography has been performed in 500 patients with mitral stenosis, 250 of whom underwent mitral commissurotomy. With the usual technique, 1 to 1.2 c.c. of Joduron (70 per cent) per kilogram of body weight was injected. We have not observed any serious untoward reaction in this series of patients in spite of the fact that many had a rather severe degree of cardiocirculatory impairment. The radiograms were taken in A.P. projection at 2, 4, 6, 8, 10, 12, 14, 16, and 20 seconds after the injection of the contrast material.

Cardiac catheterization was carried out in fifty patients according to a method previously described.[2] This method and calculations for physiologic studies are those described in the American literature.

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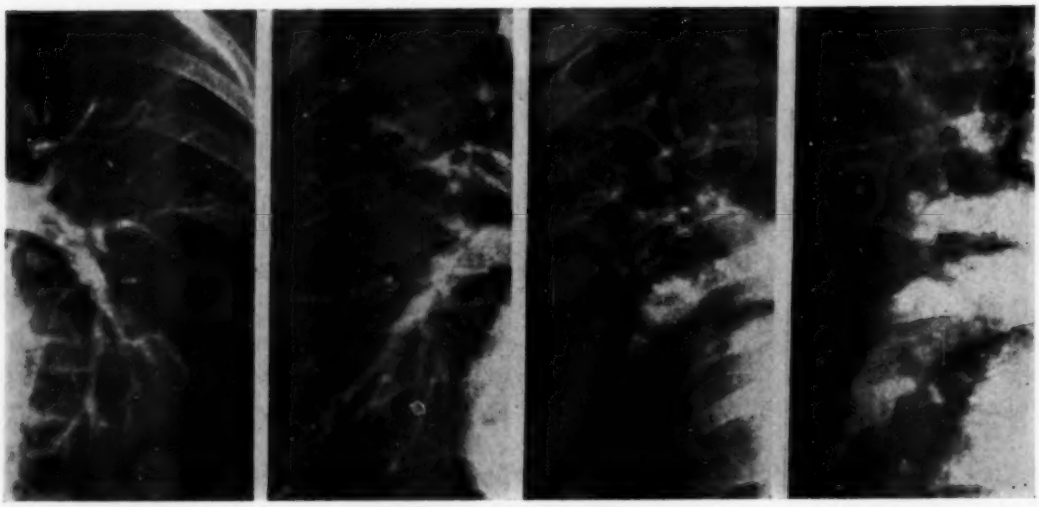
RESULTS

A. *Morphologic Aspect of the Pulmonary Circulation.*—A more or less marked enlargement of the main trunk is always present. The left and right pulmonary arteries are also usually larger than normal.

The morphologic changes of the medium sized and small pulmonic vessels are of different degrees. At times these vessels are enlarged but their outline is still regular and, as in normal subjects, their size gradually decreases toward the periphery of the lungs (Figs. 1,*B* and 3,*B*). In other instances these vessels show a very rapid change in their size immediately after their origin from the main arteries and their contours appear quite irregular (Figs. 1,*C*,*D* and 3,*C*,*D*). A tortuous course, sharp narrowings, and segmental amputations of the pulmonary vessels can also be present. These changes are particularly evident at the periphery of the lungs. In this region the arteriolar system presents itself as an intricate vascular network (Fig. 1,*C*).



A. *B.* *C.* *D.*

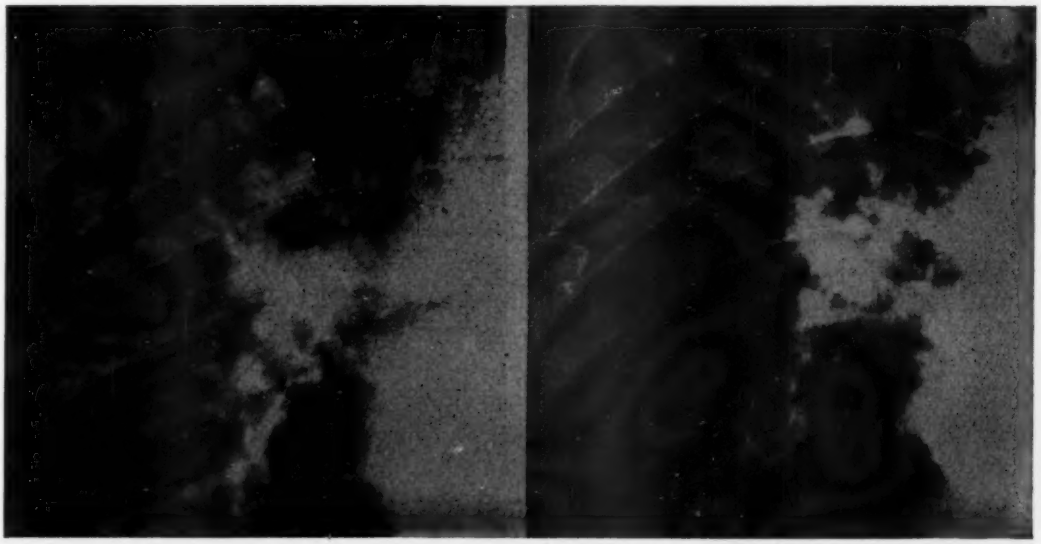
Fig. 1.—*A*, Detail of the pulmonary arterial circulation in a normal subject. The arterial ramifications are homogeneously opacified and their contours are sharply outlined. The size of the vessels decreases gradually from the hilus toward the periphery of the lungs.

***B*, Angiopulmographic aspect of the arterial pulmonary circulation in a patient with mitral stenosis and mild arterial vascular changes. Only a moderate enlargement of the arterial vascular ramifications is present, without any gross morphologic changes. The medium sized and smaller arterial vessels are still rectilinear and regular. During this stage of the disease, the venous circulation is predominantly involved (see Fig. 2,*A*).**

***C*, Patient with mitral stenosis and marked involvement of the lesser circulation. The main trunk of the pulmonary artery and its hilar and parahilar ramifications are conspicuously enlarged. The arterial vessels are abruptly narrowed and their contours are not clearly outlined, slashed, and tortuous. The peripheral branches appear as a coarse reticulum.**

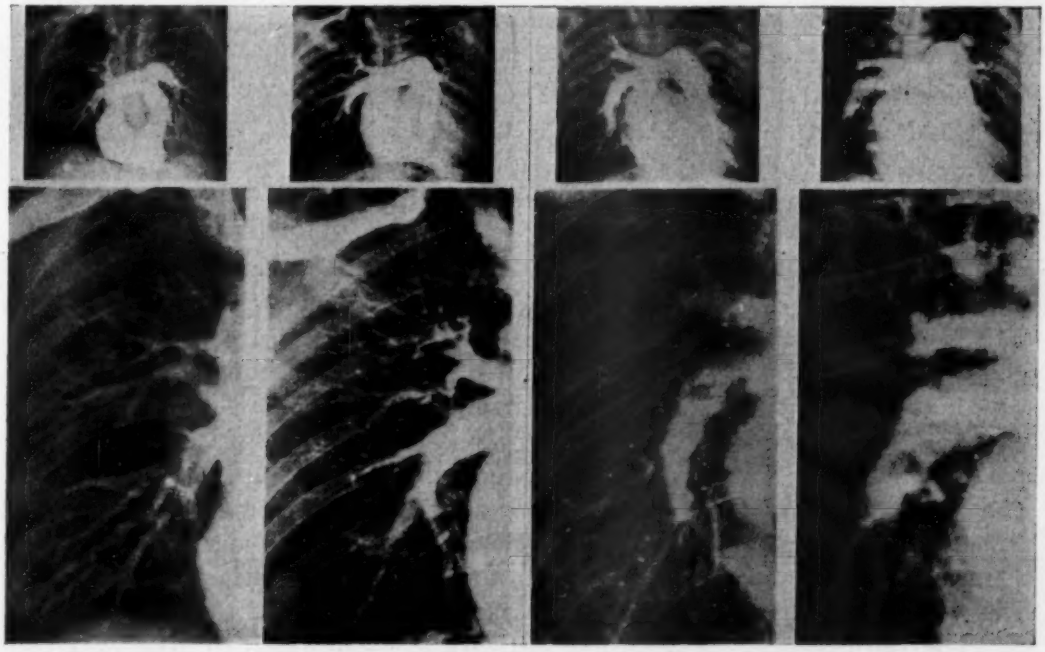
***D*, Patient with long-standing mitral stenosis and extremely serious involvement of the lesser circulation. The main pulmonary arteries are markedly dilated. The arterial vessels originating from the parahilar channels show a sharp narrowing and they appear as if they were amputated. The opacification of these vessels is nonhomogeneous. The peripheral regions of the lungs are poorly vascularized.**

During the venous phase one can see the larger than normal main pulmonary veins (Fig. 2,*A* and *B*). Very frequently, irregularly shaped dots can be seen scattered through the lung fields. The size of these dots which represent en-



A. *B.*

Fig. 2.—Detail of the pulmonary venous circulation before (*A*) and 30 days after commissurotomy (*B*). Angiopulmograms taken 8 seconds after the injection of the contrast medium. Note the enlargement of the venous vessels. Irregularly shaped dots and striae are present. A diminution of the caliber of the venous vessels is present in *B*. This finding is more evident in the parahilar region of the lung.



A. *B.* *C.* *D.*

Fig. 3.—Angiocardiograms taken at 2 seconds (*A*), 4 seconds (*B*), and 6 seconds (*C* and *D*) after the injection of the contrast material, in normal subject (*A*), in patient with mild (*B*), with severe (*C*), and with extremely severe (*D*) involvement of the lesser circulation during the course of mitral stenosis. Below: Detail of the pulmonary arterial circulation.

Results of physiologic studies (see text): *A*, T.P.R.: 132 dynes, P.V.R.: 80 dynes, M.V.R., 40 dynes; *B*, T.P.R.: 787 dynes, P.V.R.: 227 dynes, M.V.R.: 560 dynes; *C*, T.P.R.: 1894 dynes: P.V.R.: 547 dynes, M.V.R.: 1347 dynes; *D*, T.P.R.: 2561 dynes, P.V.R.: 1468 dynes, M.V.R.: 1093 dynes.

Explanation of symbols: T.P.R. = Total pulmonary resistances, P.V.R. = Pulmonary vascular resistances, M.V.R. = Mitral valvular resistances, Dynes = Dynes sec./cm.$^{-5}$

larged venous vessels may vary from 2 to 8 mm. and it gradually increases, going from the peripheral portions of the lungs toward the parahilar and hilar regions. In these cases, during the venous phase, the lungs show a coarse dotting and irregular striae.

B. *Dynamic Changes.*—In normal patients 4 seconds after the injection of the contrast medium in the cubital vein, the pulmonary artery and its main ramifications are completely emptied. By the end of the sixth second the pulmonary arterial tree is usually completely free from the injected dye, while the small venous vessels and the main pulmonic veins become progressively visualized. Visualization of the left heart chambers then follows.

In patients with mitral stenosis, as a rule from 6 to 8 seconds after the injection, the contrast medium is still present in the pulmonary artery, indicating a slowing down of the circulation during the passage through the pulmonary bed. The more serious the degree of mitral stenosis and the more marked are the anatomofunctional changes of the lesser circulation, the longer the contrast material remains in the trunk and in the main pulmonary arteries. The visualization of the smaller pulmonic vessels is also delayed and the complete arteriovenous phase lasts longer than in normal subjects. The pulmonary veins are not usually visualized before 8 to 10 seconds from the injection of the dye, and their visualization may persist as long as 15 to 20 seconds. The contrast medium then disappears very slowly from the pulmonary veins. In some patients the main pulmonary arteries may still be injected during the venous phase, so that one can see these vessels intersecting the peripheral venous twig and the large parahilar venous channels.

C. *Relationship Between Angiopulmographic, Clinical, and Hemodynamic Data.*—According to the degree of angiopulmographic morphologic and dynamic changes of the lesser circulation in mitral stenosis, we have been able to divide our patients into three main groups:

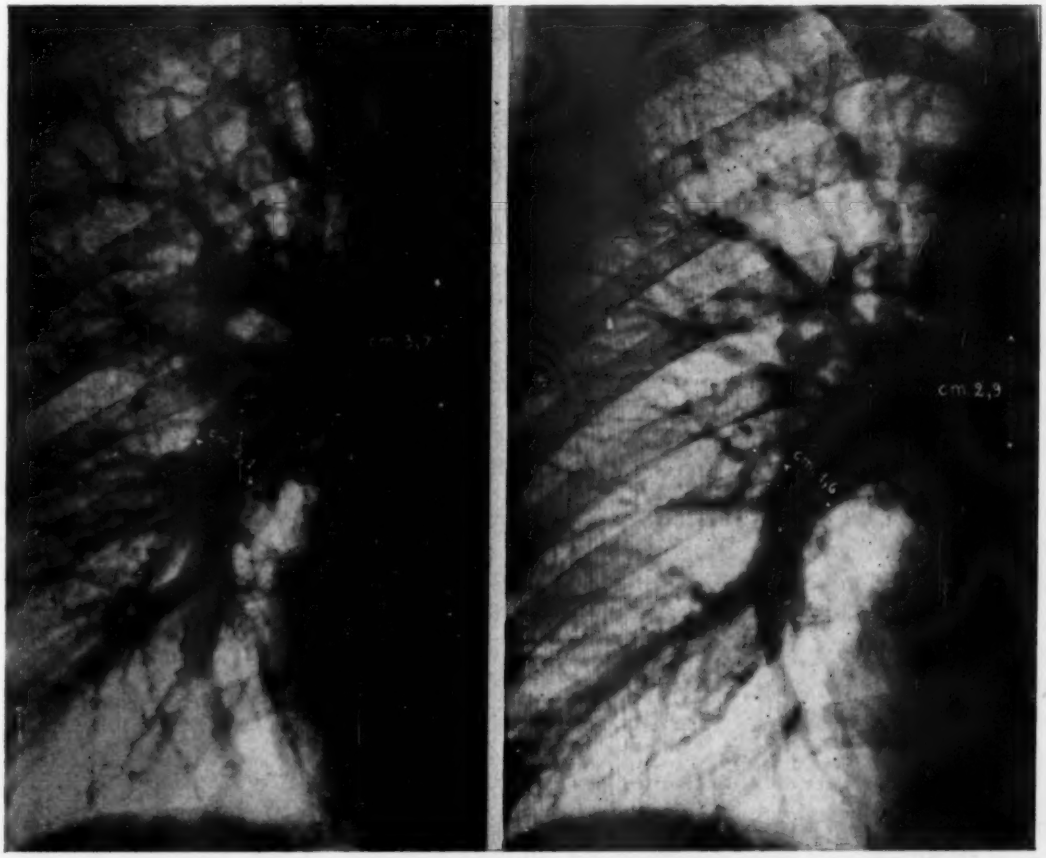
In the first group are included all those cases in which the pulmonary arterial circulation is only slightly delayed. Stasis in the venous pulmonary vessels and in the left atrium is the prominent feature in this category of patients. The vascular ramifications are regular and rectilinear, although somewhat enlarged, without any gross morphologic changes (Fig. 3,*B*).

In the second group there is a rather marked slowing down of the pulmonary arterial circulation, and the emptying of the right heart chambers is also delayed. The main pulmonary arteries and their hilar and parahilar ramifications are considerably enlarged. The smaller arterial vessels show abrupt narrowings, a tortuous course, and their borders seen to be indistinct, slashed, and irregular. The peripheral branches appear as a coarse reticulum (Fig. 3,*C*).

The third group includes those patients in which one can observe a prolonged stagnation of the contrast medium in the right heart chambers and in the pulmonary artery. The right and left pulmonary arteries are markedly dilated. The arterial vessels originating from the parahilar region show a sharp narrowing, or they may even appear as if they were amputated. Furthermore, their opacification is markedly nonhomogeneous. The peripheral regions of the lungs are poorly vascularized (Fig. 3,*D*).

The patients of the first group usually do not have a severe degree of cardiocirculatory impairment. Dyspnea on exertion is the predominant symptom and paroxysmal dyspnea rarely occurs. Neither acute pulmonary edema nor hemoptysis have been observed in patients of this group. The systolic pressure in the pulmonary artery does not exceed, as a rule, 60 mm. Hg. The mitral valvular surface is usually more than 1 c.m.^{2} and pulmonary arteriolar resistances are only slightly increased (Fig. 3,*B*).

In patients of the second and third group dyspnea is usually severe and acute pulmonary edema is a frequent feature. Hemoptysis is also not infrequent.



A. *B.*

Fig. 4.—Detail of the pulmonary arterial circulation before (*A*) and 30 days after mitral commissurotomy (*B*). Same patient as in Fig. 2. Note the diminution of the size of the right pulmonary artery (*B*).

In most of these cases the pulmonary artery pressure is elevated to a variable degree, as well as capillary pressure and pulmonary vascular and total resistances (Fig. 3,*C* and *D*). As a rule, clinical symptoms and evidence of pulmonary hypertension are most severe in those cases in which angiopulmographic changes are most marked.

Somewhat similar results have been obtained by Goodwin and co-workers.[3]

Histologic examination of the lung vessels was performed by means of lung biopsy in some of our patients. The histologic picture showed proliferation

of the connective tissue of the intima with reduction of the vascular lumen and arteriosclerosis of the media leading sometimes to a process of atrophic sclerosis. Similar changes with hypertrophy of the muscular layers and reduction of the lumina of the vessels have been also observed in the smaller pulmonary veins. These anatomic changes have been previously described by Parker and Weiss[4] and Chiovenda,[5] and others. The value of angiopulmography in assessing the degree of pulmonary vascular involvement has also been recently stressed by Bulow and associates.[6]

In some cases following commissurotomy we have observed a definite improvement in the angiopulmographic picture (Figs. 2 and 4). This observation suggests that angiopulmography might prove a valuable procedure for the evaluation of results of mitral commissurotomy.

SUMMARY

Angiopulmography has been performed in 500 patients with mitral stenosis undergoing mitral commissurotomy.

No serious untoward reactions have been observed.

According to the degree of the observed angiopulmographic morphologic and dynamic changes in the lesser circulation, the patients have been divided into three main groups.

The angiopulmographic picture correlated fairly well with clinical and hemodynamic status of the patients.

Angiopulmography appears to be a useful adjunct for the correct evaluation of patients undergoing mitral comissurotomy.

SUMMARIO IN INTERLINGUA

Examines angiopulmonographic esseva executate in 500 patientes con stenosis mitral, subjicite a commissurotomia.

Nulle serie reactiones de character negative esseva observate.

Le patientes esseva gruppate in tres classes secundo le grado del angiopulmonographicamente observate alterationes morphologic e dynamic del circulation minor.

Le constatationes angiopulmonographic se correlationava satis ben con le stato clinic e hemodynamic del patientes.

Angiopulmonographia pare esser un adjuncto utile in le evalutation correcte de patientes subjicite a commissurotomia mitral.

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THE SIGNIFICANCE OF THE PULMONARY VASCULAR BED IN CONGENITAL HEART DISEASE

I. Normal Lungs. II. Malformations of the Heart in Which There Is Pulmonary Stenosis

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INTRODUCTION

INTEREST in the pathologic physiology of congenital heart disease centered mainly around the exact structural defects within the heart until Edwards and his associates[1-3] directed attention to the lungs and the important role of the pulmonary vascular bed in governing the clinical course of congenital heart disease.

Pulmonary vascular changes occurring in association with various cardiac anomalies have been regarded by some authors as representing a coexisting anomaly of independent etiology.[4-24] This view is based principally on the lack of correlation between the degree of pulmonary vascular change and the size of the cardiac defect, the occasional presence of thrombotic lesions, and the occurrence of severe pulmonary vascular change in the absence of congenital heart disease. While the existence of "primary pulmonary hypertension" as a definite entity is recognized, the characteristic occurrence of pulmonary vascular changes of varying severity with certain types of congenital malformations of the heart suggests a causal relationship. Edwards[1-3, 25-28] has formulated the concept that, in association with congenital malformations of the heart, changes in the pulmonary vessels represent a compensatory mechanism which enables the patient to survive. As these changes are characteristically progressive, they may eventually become detrimental to the patient.

In order to clarify the relationship of pulmonary vascular changes with the type of malformation of the heart present, this study of the anatomic alterations of the pulmonary vascular bed was undertaken. It is proposed to examine this relationship in various age groups and clinical syndromes and thereby to improve our understanding of the course of the disease and aid in the rational application of corrective surgical procedures.

The lung material studied and the correlation of the findings of the clinical and anatomic data will be presented in the following sections:

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1. Normal lungs,
2. Malformations of the heart in which there is pulmonary stenosis,
3. Malformations of the heart in which a common ejectile force exists and both increased pressure and elevated blood flow may act upon the lungs,
4. Malformation in which a high pulmonary blood flow is the chief physiologic change,
5. Lesions of the left side of the heart causing obstruction of the pulmonary venous return, and
6. Transposition of the great vessels with and without pulmonary stenosis.

MATERIAL AND METHODS

For the past five years lung sections have been collected from autopsy and surgical biopsy material from a large number of patients with congenital heart disease and from more than one hundred normal patients of all ages who died of causes unrelated to the heart and lungs. Elastic tissue and hematoxylin and eosin stains were made. An arbitrary method was set up for the evaluation of the pulmonary vascular changes in small, muscular pulmonary arteries associated with, or lying clearly apart from small bronchioles. The total transverse diameter of such a vessel was measured. The thickness of each layer, adventitia, media, and intima, was recorded. Arbitrarily, the diameter of the lumen was divided by twice the thickness of the media and intima added together, thus giving a ratio of lumen size to wall thickness.

Every effort was made to insure an objective evaluation of the material. No clinical data were available at the time of the microscopic examination of the lung. Measurements were made from different areas of the lung and showed good agreement in the lumen:wall ratio obtained. Similarly, the results recorded independently by each of us checked closely in the great majority of instances. Serial sections were examined in a few cases and confirmed the consistency of this measurement. It was found that as long as the study was confined to the small muscular arteries, the size of the patient and, hence, of the vessel itself did not influence significantly the ratio obtained. Thus, while any numerical expression of a histologic change is, of necessity, an approximation, the consistency of the results obtained suggests that this method is reliable in evaluating the trend of pulmonary vascular alterations.

Graphs were constructed to correlate the microscopic and clinical data. The lumen:wall ratio was plotted against the age of the patient. Semilogarithmic paper was used to allow for a wider spread of data in the younger age groups. The clinical and laboratory data of each case were analyzed independently and the type of malformation, as well as the clinical pattern, were indicated by special symbols. In addition to the numerical determinations of the lumen:wall ratio of the small, muscular arteries, qualitative alterations in all vessels and in the lung parenchyma itself were assessed. From the characteristic combination of microscopic findings, a correct differential diagnosis relative to pulmonary pressure, magnitude of blood flow, and venous obstruction could be made in most instances without reference to the clinical summary.

I. NORMAL LUNGS

In the newborn the parenchyma of the lung has a characteristic lobular appearance. Within each lobule there are one or more bronchioles surrounded by a rather heavy layer of connective tissue which also encases a muscular pulmonary artery and thin-walled pulmonary vein. Alveoli, separated by loose connective tissue and capillaries, surround each bronchus and pulmonary artery.

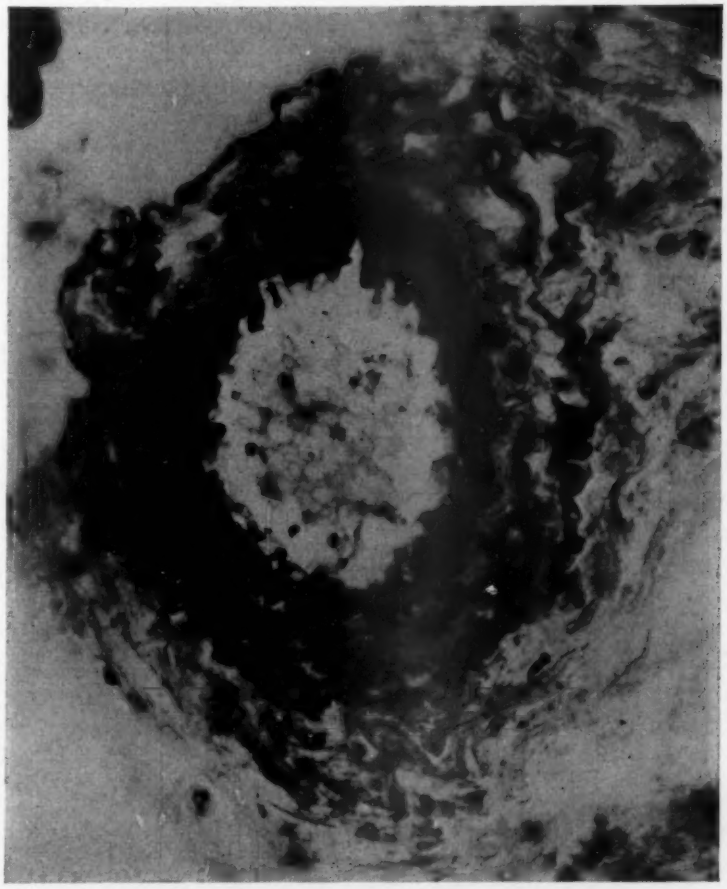


Fig. 1A.—Microphotograph of a small pulmonary artery of a normal newborn infant.

The lobular pattern of the lungs is retained after birth for variable periods of time. It may be seen for several months or may disappear within a few hours after birth. In the newborn infant many bronchial arteries are present in the walls of the larger bronchi. As the bronchi branch and become progressively smaller, the number of bronchial arteries decreases. In a study of the pulmonary vascular bed, every effort must be made to separate the pulmonary artery from a bronchial artery. In most instances this is not difficult, for the bronchial artery lies clearly within the supporting wall of the bronchus, whereas the branches of the pulmonary artery lie without.

At birth the structure of the small intrapulmonary arteries resembles that of the small arteries and arterioles of the systemic circulation.[29] However, progressive changes occur during the early months of postnatal life. Fig. 1*A* shows a photograph of a typical small muscular artery of a newborn infant. The lumen is small, frequently closed; the intima is thin; the media is thick, as is the adventitia. This vessel appears similar to a systemic artery. At 4 weeks of age (Fig. 1*B*) a definite change has taken place. The lumen is relatively and absolutely larger; the media is thinned out. At 2 years of age (Fig. 1*C*) further thinning out of the media and widening of the lumen have taken place. Except

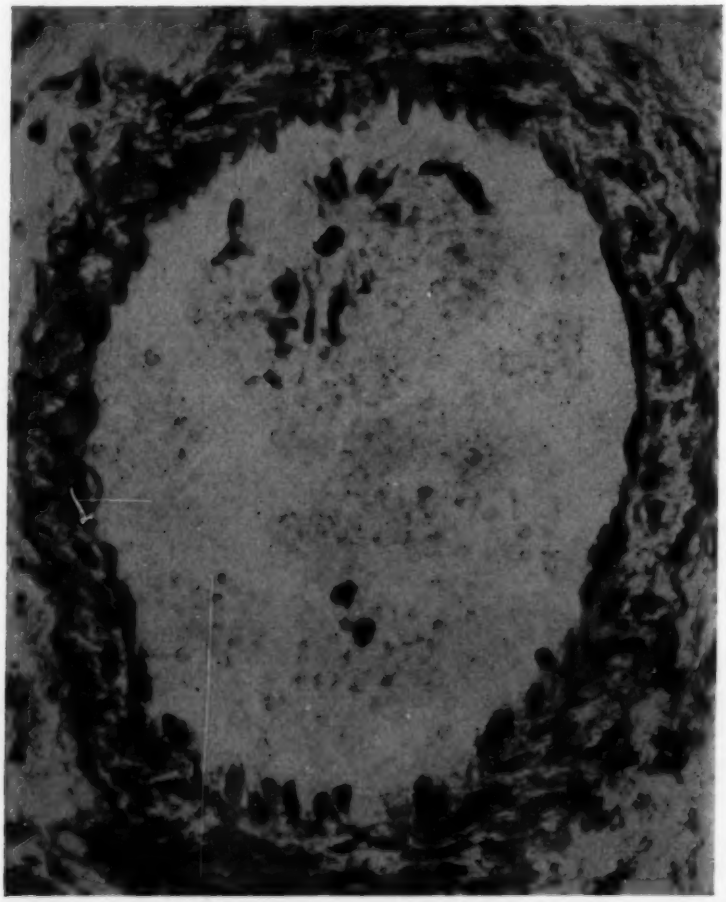


Fig. 1*B*.—Microphotograph of a small pulmonary artery of a 4-week-old child whose lungs were normal.

for the presence of an elastica interna and externa, often difficult to discern, the small pulmonary arteries look very much like small veins. Thus the tendency is for the narrow fetal arteries to become progressively wider and thin-walled.

Graph I illustrates the lumen:wall measurements obtained from patients of varying ages in whom death was due to causes unrelated to the heart and lungs and who, during life, had shown no evidence of any abnormality which might have affected the state of the pulmonary vasculature (e.g., pneumonia or other chronic pulmonary infections, asthma, nephritis). Low ratios were

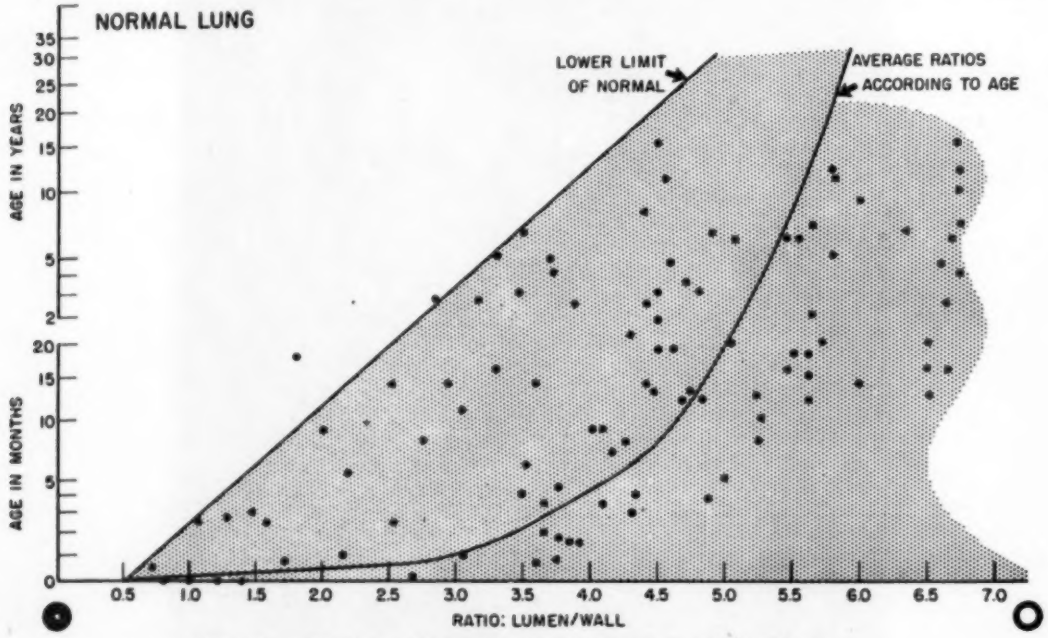
the rule at birth, but within the first few months of life considerable variation was observed. By 6 months of age some children had obtained a ratio as high as 5.0 which others did not reach even at 5 years. Almost all infants, however, had passed a ratio of 2.5 by 6 to 10 months of age. A curve constructed from the average ratios of each age group illustrates that, during the first two to three months of life, the changes in the pulmonary vascular bed are rapid and then progress more slowly. Ratios obtained from young adults demonstrate little progression in the size of the pulmonary arteries. However, in the age group of 25 to 35 years, the gradual appearance of intimal change tends to reduce the

Fig. 1*C*.—Microphotograph of a small pulmonary artery of a 2-year-old child whose lungs were normal.

lumen:wall ratio. Inasmuch as this study is chiefly concerned with congenital heart disease in children and young adults, ratios obtained from normal patients of an older age are not plotted on Graph I.

This progressive vascular change from fetal to adult life is accompanied by alterations in cardiopulmonary dynamics. Pressures obtained from the living fetus by Hamilton and his co-workers[30] demonstrated that the right and left ventricular pressures were essentially equal in the first few minutes following birth. Hamilton's physiologic data agreed with the work of Barkley,[31] Dawes,

Born, Mott, and others,[32-35] who, by means of careful animal angiocardiographic studies, have demonstrated that the fetal right ventricle supplies blood to the descending aorta through the ductus arteriosus. Lind and Wegelius[36] have confirmed this observation in the newborn human being. Such a circulatory arrangement is possible only if vascular resistance of the fetal lung is equal to or exceeds that of the systemic vascular bed. The etiology of such a high level of pulmonary pressure is usually ascribed to the presence of a collapsed lung and the distention of alveoli with fluid. Edwards and Civin have suggested that the fetal small-lumened, thick-walled pulmonary arteries play a major role in maintaining a high resistance and balancing the distribution of blood to the lungs and to the descending aorta through the patent ductus. Following birth, the progressive increase in lumen size and decrease in wall thickness results in a pro-



Graph I.—The lumen:wall ratios obtained from normal patients.

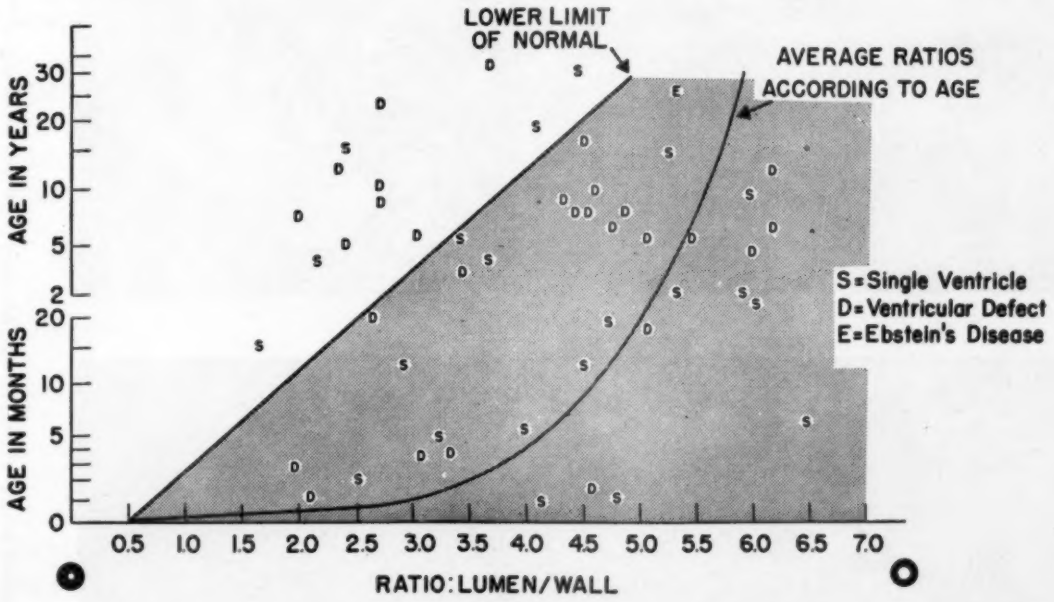
gressive fall in pulmonary vascular resistance until the normal adult state is reached, in which a pulmonary arterial mean pressure, 75 to 80 per cent lower than the systemic arterial mean pressure, suffices to propel blood through the lungs.

From the preceding discussion it becomes apparent that the pulmonary vascular bed follows a distinct and purposeful evolutionary pattern. This pattern must be taken into consideration when changes observed in the lungs of patients with congenital heart disease are evaluated.

II. MALFORMATIONS OF THE HEART IN WHICH THERE IS PULMONARY STENOSIS

Microscopic examination of the lungs of fifty patients over 2 months of age in whom a clearcut anatomic pulmonic stenosis was present revealed an essentially normal pattern of evolution of the pulmonary vascular bed (Graph II).

The small pulmonary arteries were thin-walled with wide lumens and could not be distinguished from those found in normal lungs (Fig. 2). However, in several instances, especially in patients with pulmonary atresia, an extensive bronchial collateral circulation was present. Difficulty was encountered in differentiating the branches of these bronchial vessels from true pulmonary arteries. In some sections vessels that appeared to be bronchial arteries because of their location within the wall of the bronchus itself were seen to branch and lead out into the parenchyma of the lung. Even when clearly separate from the bronchus, the position of the vessel was no longer sufficient to differentiate a bronchial from a pulmonary artery. Bronchial vessels in patients with pulmonary atresia tended to be tortuous and to appear several times on end in the same section. Since the structure of a bronchial vessel is that of a systemic vessel, the lumen:wall ratio obtained in some of the cases of pulmonary atresia was abnormally low.



Graph II.—The lumen:wall ratios obtained from patients with an established anatomic pulmonary stenosis (single ventricle—ventricular defect).

In sections obtained from patients of an older age group, pulmonary arteries containing thrombi similar to those described by Rich[37] were frequently found. Consequently, in these too, there was a reduction of lumen:wall ratio. For the most part, however, the pulmonary arteries appeared normally thin-walled and wide-lumened. The structure of the parenchyma of the lung was normal and evidence of congestive failure was lacking.

It is not surprising to find this essentially normal appearance of the lungs in patients with pulmonary stenosis. The lung is not placed under stress by any of the acute factors that tend to alter pulmonary morphology and physiology. Pulmonary artery pressure is low or normal and pulmonary blood flow is low or normal. There is no increase in left auricular pressure or pulmonary venous

Fig. 2.

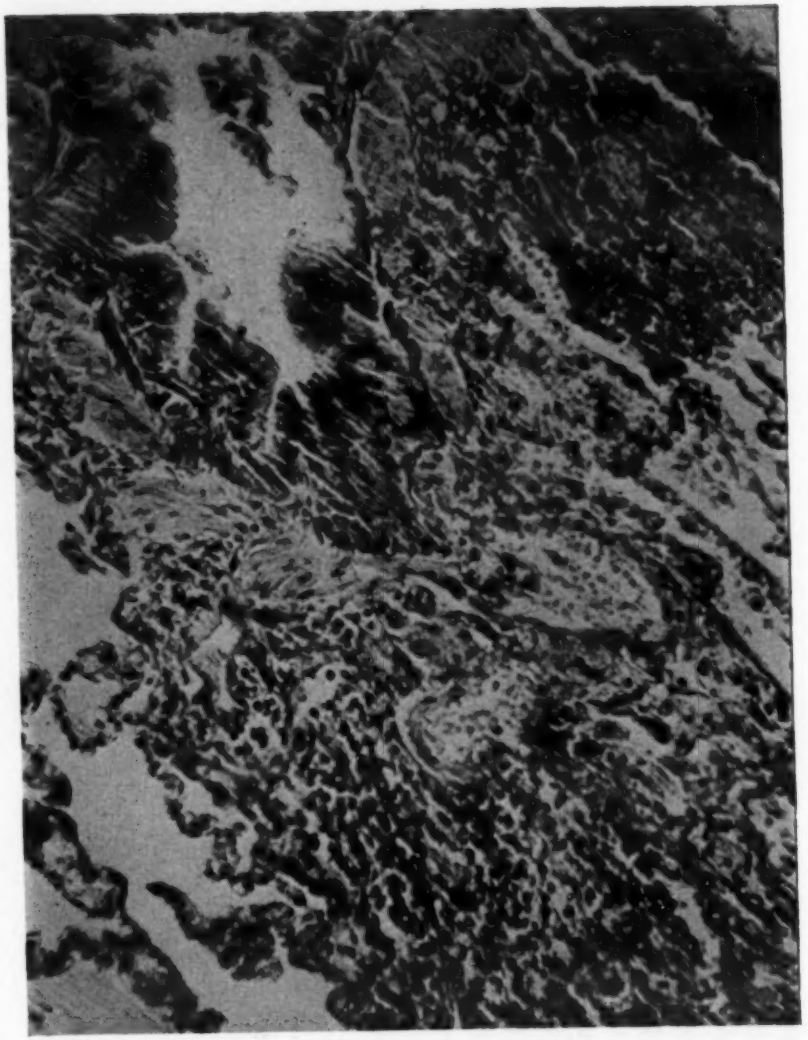


Fig. 3.

Fig. 2.—Microphotograph of a small pulmonary artery of an 11-year-old child with the tetralogy of Fallot. Note the thin wall and large lumen.
Fig. 3.—Microphotograph of a small bronchial artery from a 15-year-old boy with pulmonary atresia. Note the position of the artery within the wall of the bronchus and its spread toward the parenchyma of the lung.

pressure. Failure of the left side of the heart is rare. The factors that do influence the lung in the presence of pulmonary stenosis are related to polycythemia, anoxia, and chronic dyspnea. Polycythemia may lead to venous stasis and the production of arterial and venous thrombi. Anoxia is probably the agent leading to the development of a large collateral circulation. And finally, severe dyspnea over a long period of time may lead to a breakdown in alveolar walls and the production of areas of emphysema. Changes resulting from these factors are slow in developing and are much less striking than changes due to a high blood pressure or high blood flow.

SUMMARY AND CONCLUSIONS

1. There is a characteristic evolutionary pattern of the normal pulmonary vascular bed from the fetal to the adult state.

The small pulmonary arteries of the newborn have a thick media and adventitia and small lumen. They appear similar to systemic vessels.

Within a few months a relative and absolute thinning out of the vascular wall and widening of the lumen occurs.

As a corollary to this vascular evolution, there is a progressive decrease in pulmonary arterial resistance, so that a low arterial pressure is adequate to perfuse the lungs.

2. Patients with congenital pulmonary stenosis follow a normal evolution of the pulmonary vascular bed.

Lumen:wall ratio studies compare closely to those obtained from normal patients.

SUMMARIO IN INTERLINGUA

Le frequente association de morbo pulmono-vascular con varie congenite malformationes cardiac non es adequatemente clarificate. In le presente studio sectiones pulmonic esseva examinate ab un grande numero de patientes con congenite morbo cardiac e ab plus que cento normal patientes de omne gruppos de etate. Minor arterias pulmonar esseva mesurate, e le proportion de diametro de passage a spissitate de pariete esseva determinate. Representationes graphic esseva construite pro correlationar le datos microscopic e clinic. Le proportion passage: pariete esseva traciate como function del etate del patiente. Nostre resultatos indica que il existe un characteristic processo evolutionari del normal arbore pulmono-arterial ab le vita fetal usque al vita adulte. Como corollario de ille processo il occurre un reduction progressive del resistentia pulmono-arterial.

In le secunde parte del presente studio un analyse de patientes con stenosis pulmonar es presentate. Es constatate in le majoritate del casos un normal evolution del arbore pulmono-vascular.

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the wall of the bronchus and its spread toward the parenchyma of the lung.

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THE MITRAL PATIENT BEFORE AND AFTER SURGERY

Diagnostic—Graphic Investigations

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MITRAL commissurotomy is accepted as a corrective procedure of mitral stenosis even by those who do not believe that the valvular defect can cause a progressive cardiac failure without active myocarditis. Once serious organic damage has occurred and the orifice is so significantly reduced by scar tissue that cardiac dynamics become markedly disturbed, widening of the narrowed orifice would certainly reduce the burden of the impaired myocardium. Indications and contraindications for commissurotomy have been differently set by various groups in this country and abroad. Attempts at evaluating the results obtained by surgery are also numerous. However, the criteria of selection and the methods of evaluation are still controversial and will remain so as long as we are unable to recognize the exact degree of rheumatic activity at any given time in order to separate the mechanical effect of the mitral block from the functional disorder caused by an active myocardial lesion.

It has been repeatedly stated that both the subjective improvement revealed by decrease of exertional dyspnea and the increase of physical ability are not directly related to the results of surgery, and that they are not even related to pressure changes as revealed by cardiac catheterization.

The purpose of our study is to correlate various objective graphic findings before and after surgery with the clinical data of patients, and to evaluate the value of different diagnostic methods in the recognition of the mitral block and its modification by surgery.

In trying to evaluate the cardiac status of a patient, three diagnostic methods were selected: electrocardiography, phonocardiography, and electrokymography. To our knowledge, this is the first systematic report of studies made by means of the above-mentioned methods.

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MATERIALS AND METHODS

Twenty-one patients from 22 to 57 years of age were studied before and after mitral valve surgery. Nineteen of them were diagnosed as having predominant mitral stenosis while, in the other two, mitral regurgitation was considered predominant. The present study reports the results of graphic investigations (phonocardiography, electrokymography, and electrocardiography) and their correlation with roentgenologic, clinical, and surgical data.

Surgical Procedures.—The technique employed by the surgeon (Dr. H. D. Trace) was the following: correction of mitral insufficiency by application of a purse string around the mitral ring (1 case); mitral commissurotomy by finger fracture (17 cases); finger and knife commissurotomy (2 cases); atrial appendectomy only (1 case). The dilatation of the mitral valve was considered adequate in all the nineteen patients in which commissurotomy or finger fracture was performed.

Electrocardiography.—Electrocardiograms consisting of the three standard leads, three aV limb leads and three to seven chest V leads, were taken in all cases before and after surgery. The following data were considered: (1) Rhythm; (2) P wave: axis, duration, amplitude, and morphology; (3) QRS complex: axis, electrical position and possible rotations, intrinsicoid deflection in V_1 and V_6, pattern in V_1, R/S ratio in V_1 and V_6, and $SV_1 + RV_5$ index; (4) S-T segment and T-wave changes; (5) Digitalis effect, if any.

Phonocardiography.—All patients were systematically studied before and after surgery. The tracings were taken a few days before surgery and from three to twenty-four months after it. The phonocardiograms were recorded by means of a Sanborn Twin-Beam with "stethoscopic" and "logarithmic" methods over the routine auscultatory areas: apex, midprecordium, pulmonic, aortic, and tricuspid areas. Electrocardiograms and low frequency tracings (cardiograms) were used for timing purposes.

For interpretation and analysis of the sound tracing, the following data were considered: (1) First heart sound: amplitude and duration; (2) Second heart sound: amplitude, possible splitting; (3) Opening snap of the mitral valve: presence, distance from the second heart sound (2-O.S.); (4) Distance from the peak of R to the onset of the maximal vibration of the first heart sound (R-1); (5) Presence of murmurs: area, duration, phase, and magnitude.

Electrokymography.—In all cases, systematic electrokymographic studies of the left atrium were performed before and after surgery. The border tracings were recorded, with the patient in a sitting position, in several projections: right and left anterior obliques and right lateral position. The slit of the phototube was placed at two levels (higher and lower) in each position. If the left auricular appendage could be visualized in the posteroanterior view, a tracing was also recorded over this structure. Moreover, two densograms were also taken in the lateral projections. Therefore, from eight to nine tracings were recorded in most cases. For timing purposes, a sound tracing was simultaneously recorded. The film moved at 75 mm. per second, a speed which is adequate for

correct analysis of the time relationship of the waves. A calibrating device was used for evaluating the amplitude of the waves. A Sanborn electrokymograph and a Twin-Beam were used.

Interpretation of the tracings, made according to previously set rules,[5,6] included the following points: (1) Presence of a normal or abnormal atrial pattern (systolic plateau); (2) Presence or absence of the presystolic wave; (3) Measurement of the onset of the plateau from the first loud vibration of the first sound, and of the end of the plateau from the end of the second sound and from the opening snap, if this was present; (4) Number of projections presenting a plateau pattern.

The term "late plateau" was used whenever: (a) the onset of the ascending branch of the plateau took place from 0.10 to 0.14 second after the first vibration of the first sound; (b) both the ascending and the descending branches were oblique; and (c) the beginning of the descending branch followed the main vibration of the second sound by 0.05 to 0.08 second.

The term "early plateau" was used whenever: (a) the onset of the ascending branch of the plateau took place from 0.04 to 0.06 second after the first vibration of the first sound; (b) both the ascending and the descending branches were steep; and (c) the beginning of the descending branch followed the main vibration of the second sound by about 0.02 second.

The term "intermediate plateau" was used in intermediate cases.

Catheterization of the Right Heart.—Catheterization was done in four cases before surgery; in two of them, it was repeated after surgery. Another case had catheterization only after surgery. The pressure measurements and pulses were recorded from the right atrium, right ventricle, and pulmonary artery, and the pulmonary "wedge" pressure was also studied.

RESULTS

Out of twenty-one patients, nineteen had the preoperative diagnosis of predominant mitral stenosis, and two, that of predominant mitral regurgitation. One patient also had mild aortic stenosis; moderate tricuspid regurgitation, probably partly relative, was present in two cases.

Electrocardiography.—Thirteen out of twenty-one cases had sinus rhythm before surgery while eight were fibrillating. After surgery, nine cases were fibrillating. The following changes of the P wave were observed in the twelve cases having sinus rhythm after operation: the axis of the P wave presented a shift toward the left in six cases; toward the right, in three cases; and remained unchanged in two cases. The amplitude of P decreased in eleven cases and increased in one. The duration of P decreased in nine cases and did not change in three. There was no significant change in the morphology of the P wave after surgery, the so-called mitral configuration persisting in all the thirteen cases.

The electrical axis of QRS presented a shift toward the left in sixteen out of the twenty-one cases; toward the right in four (Cases 5, 6, 13, 16; Table I); there was no change in one case.

The electrical position of the heart before surgery was: vertical in fourteen cases, semivertical in three, semihorizontal in one, horizontal in one, intermediate in one, and undetermined in one. After surgery, the electrical position was still vertical in six cases, while it became semivertical in eight, intermediate in four, horizontal in two, and remained undetermined in one.

Six cases out of the twenty-one had a marked clockwise rotation before surgery; two had a moderate rotation, and one a mild rotation. Seven cases had a normal transitional zone (no rotation) and, in one, the rotation could not be determined for technical reasons. After surgery, only one patient showed a marked clockwise rotation; this patient also had kyphoscoliosis. One patient had a moderate clockwise rotation, and eight had a mild rotation, while the others had no rotation.

The general ventricular pattern revealed definite right ventricular hypertrophy in five cases out of twenty-one; of moderate right ventricular hypertrophy (incomplete right bundle branch block) in three; of combined ventricular hypertrophy in one; of left ventricular hypertrophy in three; and was normal in the remaining nine cases. After surgery, moderate, but definite evidence of right ventricular hypertrophy was present in two cases; incomplete right bundle branch block, in six; combined ventricular hypertrophy in two; and a normal ventricular pattern in eight patients. Left ventricular hypertrophy was still present in three cases, as before surgery.

All the twenty-one patients were taking digitalis before surgery at the time of recording of the tracings while, after surgery, only fourteen still required it.

Phonocardiography.—In determining the exact amplitude of the heart sounds, the figures were corrected corresponding to the amplification used during recording.*

In twenty out of twenty-one patients, the first sound had a high amplitude at the apex before surgery. In seventeen of them, there was a marked decrease of the first sound after surgery, while a minimal increase was noted in two (Cases 5 and 9, Table II); only one patient (Case 7, Table II) had a first sound of low amplitude before commissurotomy and a marked increase after the operation.

The duration of the first sound increased in seventeen cases after surgery, decreased in three, and was unchanged in one.

The amplitude of the second pulmonic sound decreased after surgery in fourteen out of twenty-one cases, increased in six, and did not change in one. There was splitting of the second sound in all twenty-one cases before surgery and in nineteen cases after it.

The interval between second sound and opening snap (2-O.S.) markedly increased after surgery in nineteen out of twenty-one patients (Table II), and slightly decreased in two (Cases 7 and 15). One of the latter (Case 15) was diagnosed as having predominant mitral regurgitation and this was confirmed during surgery.

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*Correction was made by a ratio between amplitude of sound and electric calibration.

TABLE I. ELECTROCARDIOGRAM

NO.	NAME SEX AGE	RHYTHM	P WAVE				QRS COMPLEX									T WAVE		DIGITALIS
			AXIS	DURATION	AMPLITUDE	FORM	AXIS	ELECTRICAL POSITION	ROTATION	INTR. DEFL. V_1	INTR. DEFL. V_6	PATTERN V_1	R/S V_1	R/S V_6	GENERAL VENTRICULAR PATTERN	AXIS	PATTERN V_1	
1	R.M. F 30	S S	+8 +50	0.10 0.10	2.50 1.30	M M	+110 +80	V V	Clockwise +++ ++	0.035 0.060	0.025 0.025	R rSr′	R Incomp. R.B.B.B.	1 4.5	R.V.H. Incomp. R.B.B.B	−30 −10	Negative Negative	Yes No
2	K.I. F 26	A.F. A.F.	— —	— —	— —	— —	+105 +88	V V	Clockwise +++ +	0.030 0.020	0.021 0.020	qR qr	qR qr	0.2 6	R.V.H. R.V.H. ↓	? ?	Negative Biphasic	Yes Yes
3	R.B. F 30	S S	+48 +30	0.12 0.10	2.00 1.50	M M	+117 +54	V V	Clockwise +++ +++	0.040 0.020	0.015 0.030	R rS	R 1	1.3 1.8	R.V.H. R.V.H. ↓	+30 +50	Isoelectric Positive	Yes No
4	C.S. F 30	S S	+60 +53	0.11 0.10	2.70 1.25	M M	+73 +60	V SV	Clockwise + None	0.020 0.015	0.035 0.035	rS rS	0.30 0.25	qR qR	Normal Normal	+54 +60	Positive Positive	Yes No
5	T.A. F 38	S S	+65 +65	0.11 0.10	3.50 2.50	M M	+46 +70	SV SV	Clockwise + None	0.020 0.005	0.030 0.040	rS rS	0.25 0.10	qR qR	Normal Normal	+56 +54	Biphasic Biphasic	Yes Yes
6	K.M. F 57	A.F. A.F.	— —	— —	— —	— —	+70 +72	V SV	Clockwise + None	0.015 0.015	0.450 0.060	rS rS	0.05 0.14	qR qR	L.V.H. L.V.H.	? ?	Biphasic Biphasic	Yes Yes
7	L.D. F 41	S S	+40 −25	0.12 0.12	1.30 1.00	M M	+81 +60	V SV	None None	0.025 0.060	0.035 0.030	rS rSr′	0.9 Incomp. R.B.B.B.	4 1.5	Normal Incomp. R.B.B.B.	+50 +45	Positive Negative	Yes Yes
8	C.C. F 40	S S	+71 +58	0.12 0.12	2.7 1.5	M M	+78 +58	V 1	? Clockwise +	? 0.250	? 0.035	? rS	? 0.3	? 12	Normal Normal	+77 +73	? Biphasic	Yes No
9	Q.D. M 22	S S	+65 +60	0.11 0.10	2.2 2.0	M M	+95 +95	V V	None None	0.030 0.015	0.040 0.040	rS rS	1.75 1	qR qR	Normal Normal	+63 +65	Positive Biphasic	Yes Yes
10	Z.M. F 40	S S	+55 +55	0.12 0.11	2.3 2.0	M M	+105 +55	SV U	Clockwise +++ None	0.070 0.025	0.025 0.035	rSr rS	Incomp. R.B.B.B. 0.20	rS qRs	Incomp. R.B.B.B. Normal	+75 +65	Negative Biphasic	Yes No
11	C.D. F	S	+52	0.11	2.0	M	+107	V	Clockwise	0.020	0.025	rS	1.0	4	Normal			

40	S	+55	0.11	2.0	M	+55	U	None	0.025	0.035	rS	0.20	qRs	Normal	+45	Biphasic	Yes
11	C.D. F	S	+52	0.11	2.0	M	+107	V	Clockwise +++	0.020	0.025	rS	1.0	4	Normal	+45	Biphasic	Yes
	36	S	+60	0.10	3.0	M	+78	SV	+	0.020	0.035	rS	1.0	6	Normal	+58	Negative	No
12	K.A. F	S	+30	0.11	3.0	M	+95	V	Clockwise ++	0.040	0.025	Rs	5.0 Incomp.	qRs	R.V.H. Incomp.	−30	Negative	Yes
	33	S	+50	0.09	1.5	M	+48	SV	+	0.070	0.035	Rsr′	R.B.B.B.	qR	R.B.B.B.	+46	Negative	No
13	S.M. M	S	+30	0.12	2.0	M	+45	H	None	0.030	0.045	Rs	2.0	qR	C.V.H.	+60	Biphasic	Yes
	37	S	+30	0.11	1.0	M	+60	H	None	0.030	0.040	Rs	2.0	qR	C.V.H.	+30	Negative	Yes
14	S.P. F	A.F.	—	—	—	—	+60	SV	None	0.020	0.040	rS	0.50	qR	Normal	?	Biphasic	Yes
	41	A.F.	—	—	—	—	+44	SV	None	0.020	0.040	rS	0.28	qR	Normal	?	Biphasic	Yes
15	G.H. M	S	+58	0.11	1.0	M	+45	SH	None	0.015	0.055	rS	0.50	qR	L.V.H.	?	Positive	Yes
	43	A.F.	—	—	—	—	+35	H	None	0.020	0.055	rS	0.40	qR	L.V.H.	?	Positive	Yes
16	B.S. M	A.F.	—	—	—	—	+70	U	Clockwise +	0.010	0.040	rS	0.12	qR	L.V.H.	?	Positive	Yes
	38	A.F.	—	—	—	—	+80	U	+	0.010	0.055	rS	0.05	qR	L.V.H.	?	Positive	Yes
17	S.F. F	A.F.	—	—	—	—	+90	V	Clockwise +	0.060	0.040	Rs	2.0	1.0	R.V.H.	?	?	Yes
	52	A.F.	—	—	—	—	+30	1	+	0.035	0.040	rS	0.75	qR	C.V.H.	?	?	Yes
18	B.A. F	A.F.	—	—	—	—	+100	V	Clockwise +	0.040	0.020	qR	qR Incomp.	7.0	Normal Incomp.	?	Biphasic	Yes
	41	A.F.	—	—	—	—	+90	V	+	0.080	0.040	rSr	R.B.B.B.	5.0	R.B.B.B.	?	Biphasic	Yes
19	S.J. F	S	+30	0.12	1.5	M	+100	V	Clockwise +++	0.035	0.025	rS	0.55	0.35	Normal	−30	Negative	Yes
	26	S	+5	0.09	1.0	M	+30	SV	+	0.020	0.025	rS	0.50	qR	Normal	+50	Positive	Yes
20	S.B. F	A.F.	—	—	—	—	+43	I	Clockwise +	0.065	0.025	rSr′	Incomp. R.B.B.B.	5.5	Incomp. R.B.B.B.	?	Negative	Yes
	42	A.F.	—	—	—	—	+28	I	+	0.070	0.030	rSr′	Incomp. R.B.B.B.	6.5	Incomp. R.B.B.B.	?	Negative	Yes
21	M.M. F	A.F.	—	—	—	—	+80	V	Clockwise ++	0.020	0.030	rSr	Incomp. R.B.B.B.	8.0	Incomp. R.B.B.B.	?	Biphasic	Yes
	40	A.F.	—	—	—	—	+50	V	None	0.015	0.040	rSr	Incomp. R.B.B.B.	qR	Incomp. R.B.B.B.	?	Biphasic	Yes

Intr. Defl. = Intrinsicoid deflection; S = sinus; A.F. = auricular fibrillation; Incomp. R.B.B.B. = incomplete right bundle branch block; R.V.H. = right ventricular hypertrophy; L.V.H. = left ventricular hypertrophy; C.V.H. = combined ventricular hypertrophy.

The distance from the peak of the ventricular complex to the first sound (R-1st) decreased in twenty out of twenty-one cases and increased in one (Case 15, Table II).

A systolic murmur was present at the apex in every patient before surgery. This murmur was loud in the two cases with predominant mitral regurgitation; it was moderate in six cases; and it was faint, short, and early-systolic in thirteen patients. After surgery, the murmur disappeared in two cases, became fainter and shorter in eleven, and decreased in the other eight cases.

Twelve out of the nineteen patients with mitral stenosis had a presystolic murmur before surgery, while the others were fibrillating and had a long diastolic murmur. After surgery, the murmur disappeared in one case; it became of lesser amplitude and shorter in all the others.

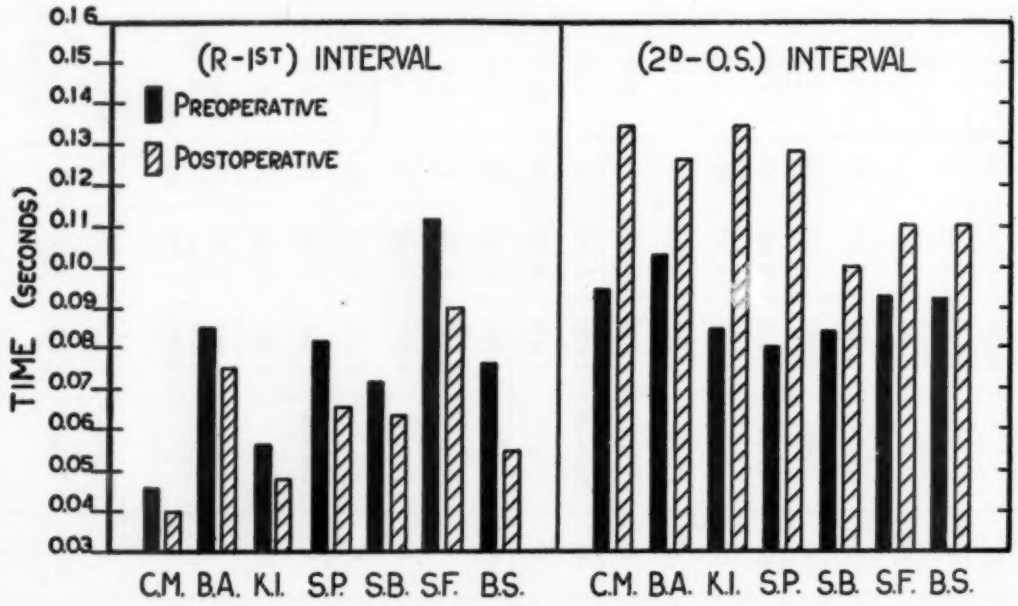

Fig. 1.—Changes of the two intervals (from R to first sound, and from second sound to the opening snap) before and after commissurotomy in cases with atrial fibrillation. The measurements have been made in cycles of corresponding length, equivalent to a heart rate of 80 to 100 per second. Shortening of *R-1st* and prolongation of *2-D.O.S.* is apparent in all cases.

The murmurs over the other areas were mostly transmitted from the apex, and either decreased or disappeared after surgery. Even in Patient 4, who had aortic stenosis, the murmur became less evident. A pulmonic early-diastolic murmur appeared shortly after surgery in two cases (6 and 21, Table II).

Electrokymography.—A systolic plateau over the left atrium was present in all the twenty-one cases before and after surgery. Before surgery, this plateau appeared in only one projection in two cases; in several projections in nineteen cases; and in all projections in the two other cases (Table III). After surgery, the plateau appeared only in one projection in one patient; in several projections in twelve cases; and in all projections in eight cases. There was an early plateau in one case (Fig. 3), an intermediate plateau in three cases, and a late plateau in seventeen cases (Fig. 4). After surgery, there was a late plateau in only three cases, an intermediate plateau in four, and an early plateau in fourteen.

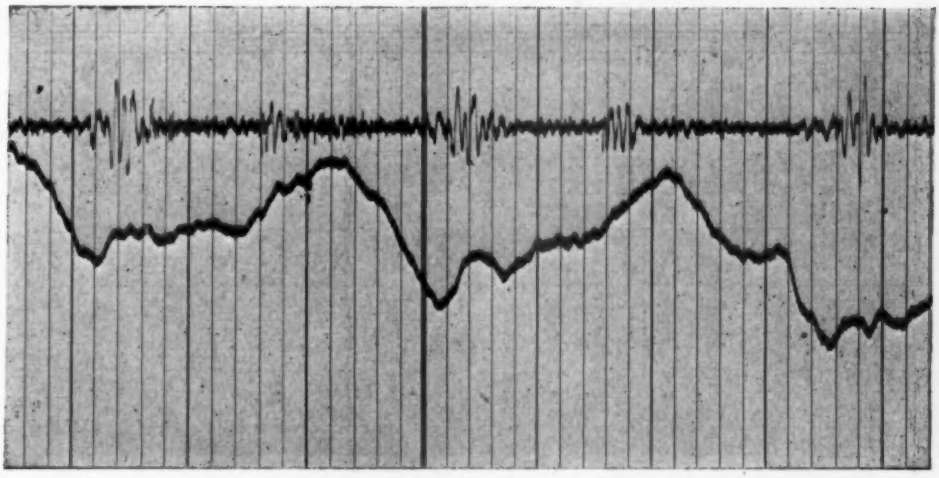

Fig. 2.—The electrokymographic pattern of the left atrium in normal subjects (simultaneous phonocardiogram).

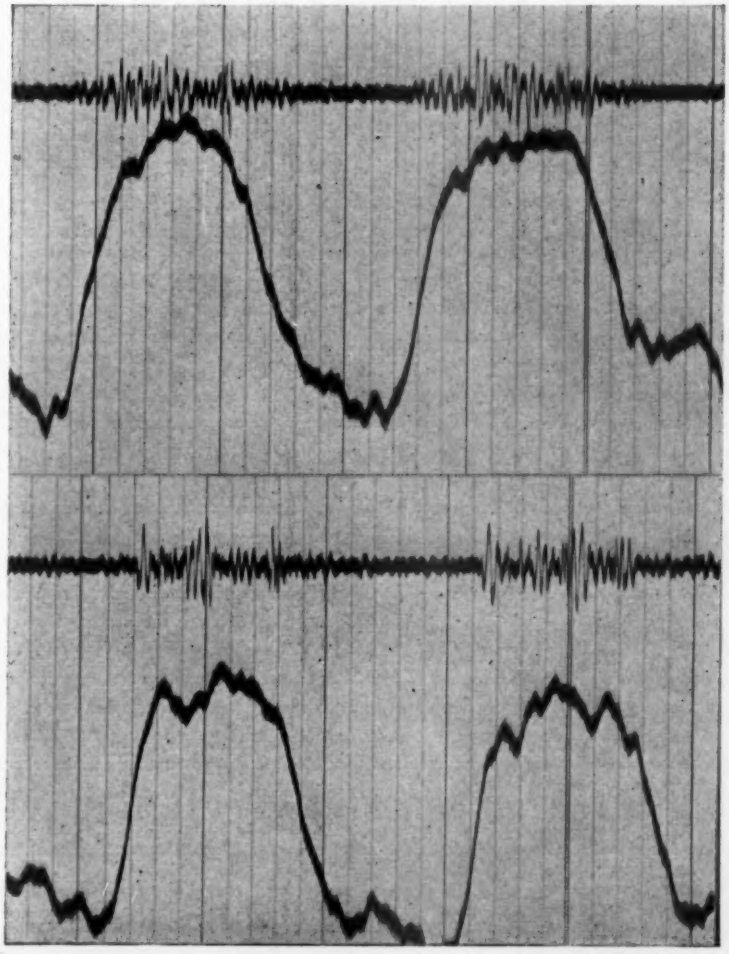

Fig. 3.—The electrokymographic pattern of the left atrium in severe mitral insufficiency (early systolic plateau). Two tracings (high and low) in LAO.

TABLE II. PHONOCARDIOGRAM

NO.	NAME SEX AGE	FIRST SOUND		SECOND SOUND		OPENING SNAP		R-1	MURMURS			
		AMPLITUDE	DURATION	AMPLITUDE	SPLITTING	PRESENCE	2-O.S.		APEX	PULMONIC AREA	AORTIC AREA	TRICUSPID AREA
1	R.M. F 30	50 (5.0) 39 (4.3)	0.09 0.08	38 (2.5) 23 (2.37)	Yes Yes	Yes Yes	0.08 0.10	0.05 0.03	Faint, short systolic, presystolic, and diastolic murmurs None	Faint systolic None	None None	None None
2	K.I. F 26	46 52 (6.5)	0.06 0.08	80 34	Yes Yes	Yes Yes	0.07 0.09	0.06 0.04	Faint, short, early systolic and all diastolic murmurs Faint, short, early systolic and shorter diastolic murmurs	Faint systolic Moderate systolic	None Faint systolic	None None
3	R.B. F 30	37 (9.2) 28 (3.5)	0.08 0.10	29 (2.6) 18 (2.12)	Yes Yes	Yes Yes	0.07 0.09	0.07 0.04	Faint, short, early systolic and presystolic murmur Faint, short, early systolic and shorter presystolic murmurs	Faint systolic Faint systolic	None None	None None
4	C.J. F 33	56 (5.6) 28 (2.0)	0.07 0.08	18 (2.2) 21 (1.3)	Yes Yes	Yes Yes	0.11 0.10	0.04 0.03	Moderate, short, early systolic, diastolic, and presystolic murmurs Faint, short, early systolic, faint diastolic, and presystolic murmurs	Faint systolic Faint systolic	Moderate systolic Moderate systolic	Faint systolic Faint systolic
5	T.A. F 38	38 (2.7) 45 (2.8)	0.09 0.09	25 (4.1) 21 (1.6)	Yes Yes	Yes Yes	0.06 0.09	0.08 0.03	Moderate, short, early systolic, diastolic, and presystolic murmurs Faint, short, early systolic, shorter diastolic, and presystolic murmurs	Faint systolic None	Faint systolic None	None None
6	K.M. F 57	36 (3.6) 10 (1.6)	0.10 0.11	26 (5.2) 36 (6.0)	Yes Yes	Yes Yes	0.10 0.11	0.03 0	Loud, all-systolic and diastolic murmurs Moderate, all-systolic and diastolic murmurs	Faint systolic Moderate systolic Moderate early diastolic	Moderate systolic Faint systolic	Faint systolic Faint systolic
7	L.D. F 41	12 (2.4) 36 (5.1)	0.08 0.08	18 (3) 12 (4)	Yes Yes	Yes Yes	0.06 0.08	0.06 0.04	Faint, short, early systolic and presystolic murmurs Faint systolic, shorter presystolic murmurs	Faint systolic Faint systolic	Faint systolic Faint systolic	Faint systolic Faint systolic

8	C.C. F 40	29 (4.9) 25 (3.5)	0.08 0.10	38 (3.8) 38 (0.6)	Yes Yes	Yes Yes	0.08 0.10	0.06 0.05	Faint, short, early systolic, diastolic, and presystolic murmurs Fainter systolic, diastolic, and presystolic murmurs	Faint systolic Faint systolic	None None	None None
9	Q.D. M 22	33 (6.6) 48 (6.8)	0.06 0.10	18 (1.4) 30 (1.8)	Yes Yes	Yes Yes	0.09 0.13	0.07 0.05	Faint, short systolic and presystolic murmur No systolic—shorter presystolic murmur	None None	Faint systolic Faint systolic	Faint systolic Faint systolic
10	Z.M. F 40	62 (5.1) 36 (5.1)	0.10 0.12	54 (4.5) 22 (0.8)	Yes Yes	Yes Yes	0.06 0.08	0.08 0.07	Moderate systolic, diastolic, and presystolic murmurs Faint, short systolic, shorter diastolic, and presystolic murmurs	Faint systolic Faint systolic	Faint systolic None	None None
11	C.D. F 36	42 (6) 40 (4)	0.07 0.10	36 (3.6) 21 (2.3)	Yes Yes	Yes Yes	0.08 0.10	0.07 0.05	Faint, short, early systolic and presystolic murmur Faint, short systolic and faint presystolic murmur	None None	Faint systolic None	Faint systolic None
12	K.A. F 33	85 (14) 70 (11)	0.08 0.10	17 (3.4) 22 (2.4)	Yes Yes	Yes Yes	0.06 0.10	0.08 0.07	Faint systolic, all diastolic, and presystolic murmurs Faint systolic, shorter diastolic, and presystolic murmurs	Faint systolic None	Faint systolic Faint systolic	Faint systolic None
13	S.M. M 37	21 (3.5) 20	0.07 0.07	18 (1) 22	Yes Yes	Yes Yes	0.10 0.13	0.05 0.04	Moderate, early systolic, diastolic, and presystolic murmur Faint, early systolic, diastolic, and presystolic murmurs	Faint systolic Faint systolic	Faint systolic Faint systolic	Faint systolic and diastolic Faint systolic and diastolic
14	S.P. F 41	20 (2.0) 50 (1.9)	0.08 0.09	34 (3.7) 52 (4.3)	Yes Yes	Yes Yes	0.06 0.11	0.05 0.02	Moderate, all-systolic and diastolic murmurs Moderate, shorter systolic; shorter diastolic murmurs	Faint systolic Faint systolic	Faint systolic Faint systolic	Faint systolic Faint systolic
15	G.H. M 43	34 (6.8) 32 (4.5)	0.07 0.09	16 (1) 21 (3.5)	Yes Yes	Yes Yes	0.08 0.07	0.04 0.06	Loud, all-systolic murmur Moderate, irregular systolic murmur	Faint systolic Faint systolic	Faint systolic Faint systolic	Faint systolic Faint systolic
16	B.S. M 38	36 (3.0) 20	0.10 0.13	46 (3.0) 54 (1.5)	Yes Yes	Yes Yes	0.09 0.12	0.06 0.04	Moderate, early systolic, and all diastolic murmurs Faint, early systolic; faint diastolic murmur	Faint systolic Faint systolic	Faint systolic Faint systolic	None None

TABLE II.—CONT'D

NO.	NAME SEX AGE	FIRST SOUND		SECOND SOUND		OPENING SNAP		R-1	MURMURS			
		AMPLITUDE	DURATION	AMPLITUDE	SPLITTING	PRESENCE	2-O.S.		APEX	PULMONIC AREA	AORTIC AREA	TRICUSPID AREA
17	S.F. F 52	36 (6.0) 36	0.11 0.13	45 (4.0) 36	Yes Yes	Yes Yes	0.08 0.10	0.06 0.04	Faint, short, early systolic, and all diastolic murmurs Faint, short, early systolic, and shorter diastolic murmurs	Faint systolic Moderate systolic	Moderate systolic Faint systolic	Faint systolic None
18	B.A. F 41	50 (8.3) 30 (1.6)	0.07 0.18	48 (12) 34 (2.8)	Yes Yes	Yes Yes	0.08 0.12	0.08 0.07	Faint, short, early systolic, and all diastolic murmurs Faint, short, early systolic, and short diastolic murmurs	Faint systolic Faint systolic	None None	None None
19	S.J. F 26	40 (10) 42 (6)	0.07 0.09	29 (7.6) 29 (3.3)	Yes Yes	Yes Yes	0.08 0.11	0.08 0.06	Faint, short, early systolic, all diastolic, and loud, presystolic murmurs Faint, short, early systolic, faint diastolic, and faint presystolic murmurs	Faint systolic None	Faint systolic None	Faint systolic None
20	S.B. F 42	36 (4.5) 28 (4.6)	0.10 0.12	40 (4.4) 30 (5)	Yes Yes	Yes Yes	0.10 0.09	0.06 0.05	Faint systolic, moderate diastolic murmurs Faint, early systolic, and faint diastolic murmurs	Faint systolic None	None None	Faint systolic None
21	M.M. F 40	28 (7.0) 40 (2.3)	0.08 0.14	28 (4.6) 50 (8.3)	Yes No	Yes Yes	0.06 0.10	0.06 0.015	Faint, short, early systolic murmur; loud all diastolic Faint, early systolic, moderate diastolic murmurs	Faint systolic Faint systolic; moderate, early diastolic	None None	Faint systolic and diastolic Faint systolic and diastolic

Numbers in parentheses measure the ratio of the amplitude of the sound to the degree of amplification.

Surgical Findings.—A tight mitral stenosis, admitting only one-half to one tip of the surgeon's finger was present in ten patients; marked stenosis (one-half to one finger) was found in three cases; moderate stenosis (one finger), in three cases; some degree of stenosis accompanying the predominant insufficiency of the valve was found in the others. Before surgery, a regurgitant jet of blood was felt on exploration of the mitral valve with an ungloved index finger seven times. The regurgitation was considered as marked in two cases (6 and 15, Table III), moderate in four (Cases 13, 14, 16, and 17; Table III), and minimal in one case (20).

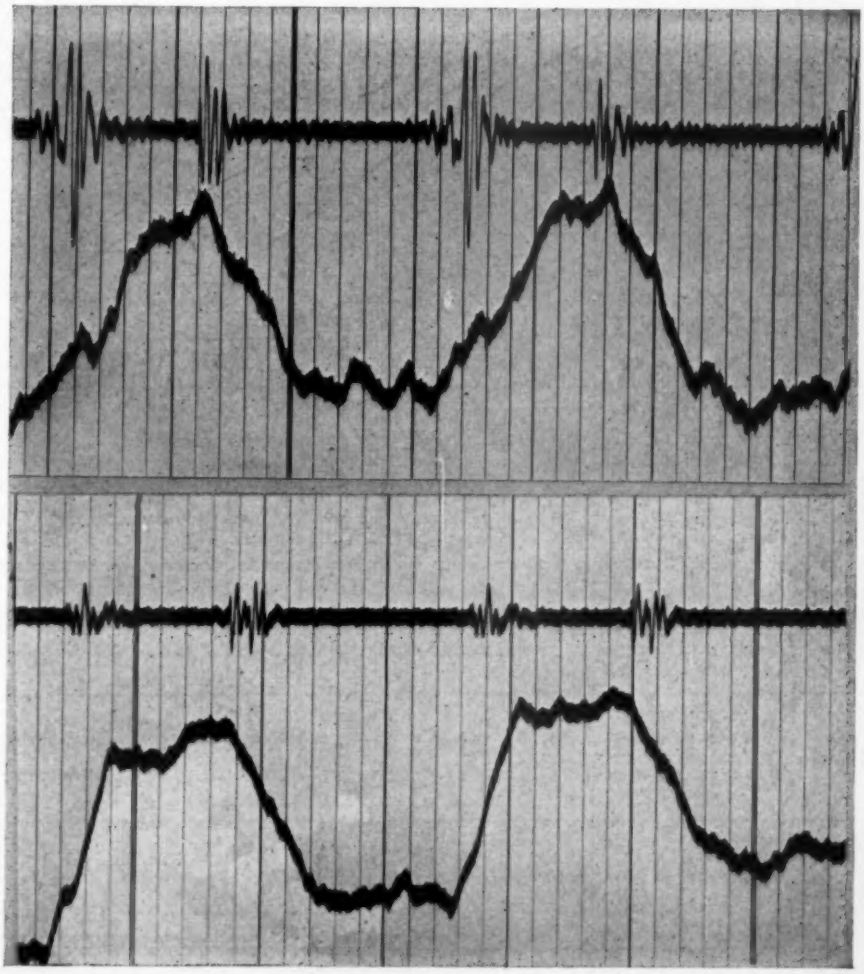

Fig. 4.—*A*, Before surgery. Electrokymographic pattern of the left atrium in severe mitral stenosis with moderate insufficiency (late systolic plateau). *B*, Same case after surgery (early systolic plateau).

After surgery, the regurgitation seemed reduced in one case (a purse string was placed around the mitral ring) and it disappeared in one (Case 17, Table III) who had a moderate regurgitation. No significant change in the regurgitant jet was felt in the other five patients. A minimal degree of regurgitation seemed to appear in one patient (Case 12, Table III). In nine out of twenty-one patients, calcifications of the mitral leaflets were palpated.

TABLE III

NO.	NAME SEX AGE	ELECTROKYMOGRAM				SURGICAL FINDINGS			BIOPSY FINDINGS
		NO. OF TRACINGS TAKEN	NO. OF TRACINGS SYSTOLIC PLATEAU	ONSET OF PLATEAU 1-P′	END OF PLATEAU 2-P″	DEGREE OF STENOSIS	REGURGITATION	CALCIFICATION	
1	R.M. F 30	3 2	2 2	0.12 0.09	0.06 0.06	Tip of finger 2 fingers	None None	None	Endocardial fibrosis Chronic myocarditis
2	K.I. F 26	6 3	2 3	0.14 0.04	0.06 0.04	Tip of finger 2 fingers	None None	None	Chronic endocarditis Hypertrophy of myocardium Chronic pericarditis
3	R.B. F 30	6 8	3 6	0.14 0.12	0.06 0.03	½ tip of finger 2 fingers	None None	None	Myocardial fibrosis Focal pericarditis
4	C.J. F 30	4 3	4 2	0.14 0.09	0.05 0.04	1 finger 1¾ fingers	None None	None	Normal appendage
5	T.A. F 38	4 9	2 6	0.14 0.06	0.04 0.03	¾ finger 1¾ fingers	None None	None	Endocardial sclerosis
6	K.M. F 57	7 9	7 9	0.08 0.06	0.05 0.03	1½ fingers 1¾ fingers	10 c.c./beat 3 c.c./beat	None	Hypertrophy of myocardium
7	L.D. F 41	4 5	3 5	0.10 0.04	0.06 0.02	Tip of finger 2 fingers	None None	Yes	
8	C.C. F 40	4 4	3 2	0.11 0.06	0.04 0.02	1 finger 2 fingers	None None	Yes	
9	Q.D. M 22	3 3	1 3	0.12 0.06	0.06 0.02	½ finger 1¾ fingers	None None	Yes	Chronic myocarditis Aschoff bodies
10	Z.M. F 40	7 8	4 8	0.14 0.12	0.05 0.02	Tip of finger 2 fingers	None None	Yes	Endocardial sclerosis Hypertrophy of myocardium

	F 40	8	8	0.12	0.02	2 fingers	None		Hypertrophy of myocardium
11	C.D. F 36	5 2	1 2	0.12 0.06	0.06 0.02	1 finger 2 fingers	None None	None	Hypertrophy of myocardium
12	K.A. F 33	3 2	2 1	0.14 0.08	0.06 0.04	½ finger 2 fingers	None 1 c.c.	None	Hypertrophy of myocardium Myocarditis
13	S.M. M 37	4 7	2 3	0.14 0.06	0.06 0.02	Tip of finger 2 fingers	5 c.c./beat 5 c.c./beat	Yes	Myocardial hypertrophy
14	S.P. F 41	4 7	2 5	0.14 0.06	0.08 0.02	1 finger 2 fingers	5 c.c./beat 7 c.c./beat	Yes	Hypertrophy of myocardium Chronic myocarditis
15	G.H. M 43	5 4	4 2	0.06 0.04	0.06 0.02	1¾ fingers 1¾ fingers	20 c.c./beat 10 c.c.	None	Endocardial fibrosis Chronic myocarditis with hypertrophy Fatty degeneration
16	B.S. M 38	6 3	5 3	0.08 0.04	0.06 0.02	1 finger 2 fingers	5 c.c./beat 7 c.c./beat	Yes	Subendocardial fibrosis Myocardial fibrosis
17	S.F. F 52	7 8	3 6	0.14 0.08	0.06 0.04	1 finger 1½ fingers	5 c.c./beat None	Yes	Subendocardial fibrosis Hypertrophy of myocardium Chronic epicarditis
18	B.A. F 41	4 9	3 8	0.14 0.06	0.06 0.03	Tip of finger 2 fingers	None None	None	Chronic endocarditis Hypertrophy of myocardium Organized thrombi
19	S.J. F 26	7 6	5 6	0.09 0.04	0.04 0.02	Tip of finger 2 fingers	None None	None	Chronic endocarditis Hypertrophy of myocardium
20	S.B. F 42	7 3	4 1	0.12 0.04	0.06 0.02	Tip of finger 2 fingers	3 c.c./beat 3 to 4 cc./beat	Yes	Chronic endocarditis Myocardial hypertrophy Organized thrombi
21	M.M. F 40	4 4	3 2	0.14 0.12	0.08 0.04	Tip of finger 2 fingers	None	None	Hypertrophy of myocardium

Biopsy of the Atrial Appendage.—Biopsy of the atrial appendage was done in nineteen out of the twenty-one cases. The histologic findings were the following: chronic carditis and presence of Aschoff bodies in one case (Case 9, Table III); chronic carditis revealed by lymphocytic infiltration, but no Aschoff bodies, in ten cases; healed carditis in three cases; hypertrophy of myocardium in four cases; normal atrial appendage in one case.

DISCUSSION

Our studies were made on a selected group of patients. The twenty-one reported cases had a complete set of electrocardiographic, phonocardiographic, and electrokymographic tracings before and after surgery. However, our experience is based on a more numerous group which includes 389 patients with multiple graphic studies, fifty-seven of whom were operated upon.

General Considerations.—Excluded from surgery were: (a) cases with obvious combined lesions of various valves; (b) cases with active rheumatic carditis; and (c) cases with definitely predominant mitral insufficiency (two such patients were, however, submitted to surgery and are included in this study).

The coincidence between clinical-graphic diagnosis and surgical evaluation was found in the range of 80 per cent. While digital recognition of mitral stenosis by the surgeon can be considered reliable, as long as no exact measurements are required, evaluation of the degree of mitral regurgitation in cases of mitral stenosis is far less so. Possible causes of error in the surgical evaluation of mitral incompetence are the following:

A. The anesthesia of the patient and the effect of opening the chest cause tachycardia and a drop of arterial pressure.* As a result, the systolic pressure of the left ventricle becomes lower (decrease of peripheral resistance), while the atrial pressure becomes higher (tachycardia). Both factors tend to decrease the amount of blood regurgitating through the mitral valve.

B. Appreciation of a regurgitant jet is hardly quantitative: a large jet may be slow and unperceptible; a thin jet may be rapid and hit the finger with violence.

The above considerations render the 80 per cent coincidence between clinical-graphic diagnosis on the one hand, and surgical diagnosis on the other, rather remarkable. This was partly due to a preliminary stage of comparison and education of the various members of the team involved in this study.

Improvement of the patients took place in all cases. However, in our experience, a real objective and subjective change became manifest only after a period of from three to six months, the latter being the most frequent interval. One patient deteriorated about seven months after the intervention because of both recurrent carditis and excessive physical strain.

Electrocardiogram.—Before surgery, evidence of severe right ventricular hypertrophy was noted in five cases; only two patients presented this evidence after surgery. The others presented either combined hypertrophy or evidence of only moderate hypertrophy.

*The systolic pressure of our cases, recorded during surgery, was usually below 90.

Three cases presented left ventricular hypertrophy; in two cases this was due to predominant insufficiency while the other had several causes of ventricular strain. These were not changed by surgery.

The ECG was recognized as a possible guide for evaluating the decrease of right ventricular load, which is common after surgery, and the increase of left ventricular load, which may occasionally be observed.

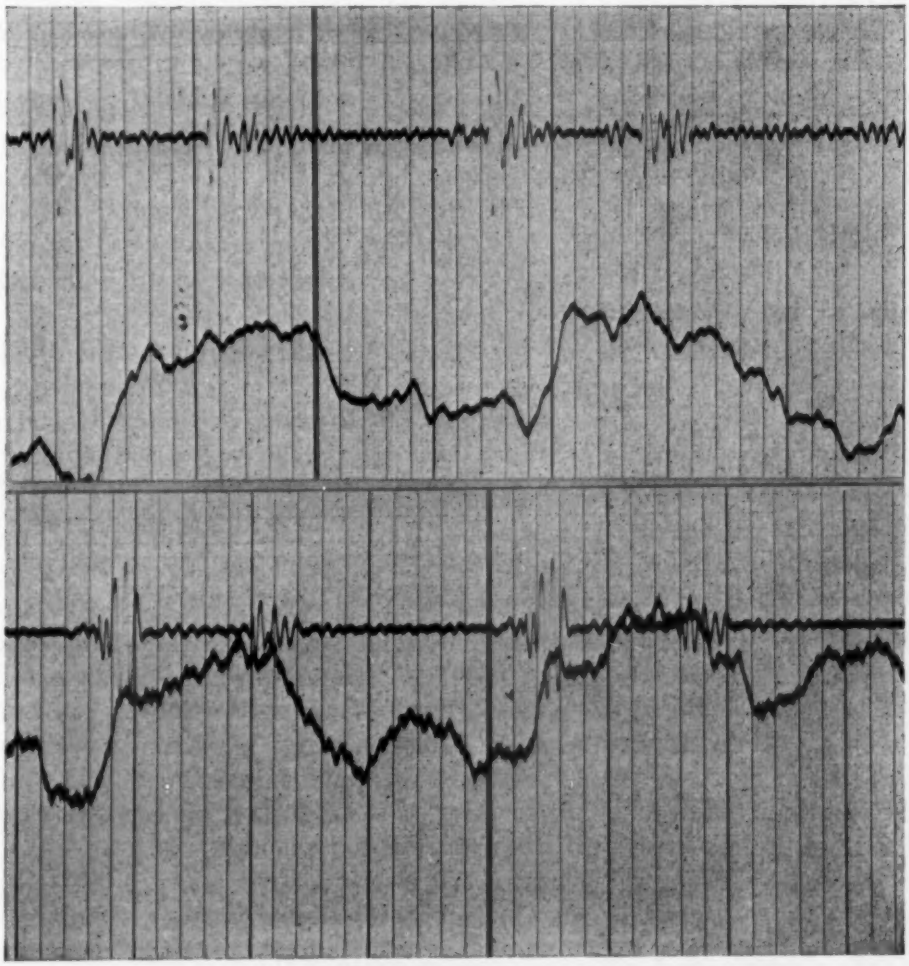

Fig. 5.—Changes of the electrokymographic pattern due to mitral commissurotomy in a case with predominant stenosis. *A*, Before surgery = late plateau, *B*, After surgery = early plateau.

Phonocardiogram.—

A. *First sound at apex:* The magnitude of the first sound decreased with surgery in seventeen cases out of twenty-one, increased in three, and was unchanged in one. It is apparent that the decrease in severity of mitral stenosis was responsible for the decreased magnitude of the first sound which followed surgery in the majority of cases. The duration of the first sound increased in seventeen cases, decreased in three, and was unchanged in one. This may be

explained by addition to the sound of some vibrations caused by a slight regurgitation (short systolic murmur ?) or by increased left ventricular dynamics due to better filling.

B. *Second pulmonic sound:* The second pulmonic sound was decreased in amplitude in fourteen cases out of twenty-one after surgery, while it was increased in six, unchanged in one. It is likely that decrease of pulmonic pressure due to decrease of mitral block lowered the right ventricular pressure in fourteen cases. It is probable that increase of pulmonic pressure, possibly due to increase of mitral insufficiency, took place in six.

C. *Intervals:* The interval 2-O.S. was found inversely proportional to the level of left atrial pressure by Wells.[1] It was found increased in nineteen out of our twenty-one cases after surgery by us (Fig. 1). One of the two remaining patients had a recurrent carditis; the other had been submitted to correction of mitral insufficiency and probably experienced some degree of stenosis. Therefore the interval 2-O.S. was recognized as a useful indicator of the results of the intervention.

The interval between R and first sound was considered as directly proportional to the level of left atrial pressure by Wells.[1] It was found decreased in twenty of our twenty-one cases after surgery, thereby revealing the decreased level of left atrial pressure; it was increased only in the case of corrected mitral insufficiency where a moderate stenosis had probably arisen (Fig. 1). This interval was also recognized as a useful indicator of the results of the intervention.

Our conclusions concerning the effect of valvotomy on both the 2-O.S. and R-1 intervals coincide with the findings of Wells[1] and Fishleder.[39]

D. *Murmurs:* The apical systolic murmur, usually faint or short, became louder or longer in three cases, and less loud or absent in sixteen cases out of nineteen of predominant mitral stenosis. It became shorter in two out of two cases of operated mitral insufficiency. These findings indicated a definite increase of insufficiency in three cases. However, the severity of the systolic murmur is a poor indicator of the severity of the regurgitation in patients with mitral stenosis and insufficiency, due to the following factors:

1. Moderate regurgitation through a narrow mitral orifice, even if the valve is incompetent;
2. High level of left atrial pressure resisting the regurgitation;
3. Inadequacy of the recording apparatus.*

The pulmonic systolic murmur became louder in three cases. This may be interpreted as due to a more rapid flow or higher pressure in the pulmonary artery. We could not decide which is true because the above three cases were not catheterized. The apical presystolic or diastolic murmur decreased in nineteen out of nineteen cases of predominant stenosis.

Phonocardiography was recognized as extremely useful in the diagnosis of mitral stenosis or insufficiency and in the evaluation of the results of surgery.

*This has been remedied recently by the method of "selective phonocardiography."[3]

Together with pulse tracings, it was useful for recognizing or excluding aortic defects. Selective phonocardiography[3] is particularly important in cases with multiple valvular lesions.

Electrokymogram.—Our main interest was based on the observation of a possible plateaulike pattern, its careful evaluation, and its interpretation. Following the study of the normal atrial pattern[5] (Fig. 2), a plateaulike pattern was described by Luisada and Fleischner in mitral valve disease[6] and interpreted as revealing mitral regurgitation. This interpretation was subsequently confirmed and accepted by several workers.[7,8,10-13,16] On the other hand, other workers [14,15,17,18] did not accept such interpretation because:

A. They found such pattern in cases declared by the surgeon as having no insufficiency.

B. They found a more typical plateau pattern in cases with clinical diagnosis of pure mitral stenosis than in others where both stenosis and insufficiency were diagnosed.

C. They found a typical plateau in cases of atrial fibrillation supposedly without mitral lesions.

D. They thought that the pattern of left atrial pressure in experimental mitral lesions (Wiggers and Feil[35]) was different from the EKY plateau described by Luisada and Fleischner.

E. They occasionally found an atypical pattern in normal subjects and interpreted it as a plateau.

Our study first tried to exclude instrumental failures like those outlined by Fleischner, Abelmann, and Buka.[20] In order to avoid errors: (a) careful placement of the slit was always done; (b) two tracings at different levels were taken in each projection; (c) at least three projections were always taken by adding a lateral to the two obliques; and (d) densograms were taken, thereby avoiding possible transmitted movements. With this technique, consistent data were found in normal subjects where a plateau pattern was *never* observed in various projections or at various levels. Only rare cases showed such pattern, and then only in one projection. As the latter had a history of infections during childhood, or had had a murmur for several years of their lives, it is possible that even these "normal" subjects did not have a normal mitral valve.

A first study dealt with the number of projections revealing a plateau pattern. The results are shown in the following scheme (Table IV).

TABLE IV. NUMBER OF PROJECTIONS REVEALING A PLATEAU PATTERN IN THE EKY OF THE LEFT ATRIUM

	BEFORE SURGERY	AFTER SURGERY
One tracing	2	1
Several tracings	17	12
All tracings	2	8
Total	21	21

Twelve cases had no change in the number of projections on account of surgery. On the other hand, one patient who had the plateau in one projection and five

patients who had it in several projections before surgery, showed it in all projections after surgery. The deduction was drawn that about one-third of the patients had greater regurgitation after surgery than before it.

A second study dealt with the relationship between the electrokymographic plateau pattern and the heart sounds (finding of either an "early" or a "late" plateau—see *technique* for definitions). The results of this study are presented in the following scheme (Table V). (See also Fig. 5.)

TABLE V. NUMBER OF CASES PRESENTING AN EARLY OR LATE PLATEAU IN THE EKY OF THE LEFT ATRIUM

	BEFORE SURGERY	AFTER SURGERY
Late	17	3
Intermediate	3	4
Early	1	14
Total	21	21

While in none of our cases did the plateau disappear, Fleischner and associates[20] found disappearance of this pattern in five of their ten cases, while the pattern was unchanged in four and appeared in one of their cases after commissurotomy. It is possible that more severe criteria of selection of our cases or different surgical techniques are responsible for this difference. In the great majority of our cases, the plateau pattern tends to occur after surgery with an earlier onset and an earlier end than prior to surgery. Given a basic, unchanging amount of regurgitation, the plateau may occur earlier for the following reasons:

A. The mitral valve is more widely open and fails to slow down the regurgitant jet.

B. The left atrial pressure becomes gradually lower and fails to oppose regurgitation.

C. The left ventricle receives a greater amount of blood in diastole and is able to raise the intraventricular pressure to a higher level.

Each of the three explanations is probably true in individual cases, and all three factors may be present in some of the cases. Whatever the explanation, one cannot avoid the impression that commissurotomy was followed by easier mitral regurgitation.

A third study was based on calibration of the EKY tracing through a device similar to that suggested by Morgan and Sturm.[37] Ten cases presented reliable calibration data both before and after commissurotomy: the systolic plateau (corrected for calibration) had the same height in eight, while it was slightly smaller in two.

Significance of the Plateau.—The objections which were raised against the interpretation of the plateau as caused by mitral regurgitation can be refuted as follows.

A. *The plateau is due to atrial fibrillation.* The plateau was found both in mitral patients with sinus rhythm and in those with atrial fibrillation, thus confirming previous findings.[6] Some nonrheumatic patients with atrial fibril-

lation may present this pattern: they have either arteriosclerotic fibrosis of the mitral valve (organic insufficiency) or myocardial fibrosis (relative insufficiency). One of the authors (A.A.L.), observed the same pattern in cases with thyrotoxicosis where a myocardial disturbance was apparent. Luisada and Magri[36] observed it in the early stages of rheumatic fever because of weakness of the myocardium and relative insufficiency. Therefore, the plateau is due to mitral regurgitation, whatever the cause of the leak.

B. *The plateau is due to raising of the mitral leaflets.* This statement contradicts a well-known principle of cardiac physiology and barely deserves refuting. If there is any raising of the valvular leaflets, this takes place only during the isometric tension period; during ejection, the a-v floor is lowered by the contraction of the free ventricular wall, of the septum, and of the papillary muscles. Evidence for this is found in the systolic collapse of the pressure tracings and of the electrokymograms of the left atrium in normal subjects. Raising of the leaflets is even more unlikely when these are fibrotic or calcified, like in mitral stenosis. The plateau of mitral patients, even if it is an "early" plateau, starts after the end of the first sound (e.g., after the end of the tension period) and ends after the second sound. This indicates a close relationship with the phase of ejection.

C. *The plateau is due to outward motion of the atrial wall which is not related to a change of atrial pressure.* In the normal heart, only one tracing of pressure has a plateaulike appearance: the tracing of intraventricular pressure. In the abnormal heart, tracings of left atrial pressures[24-32] (as well as esophagocardiograms[18,19,21-23,33,34] or electrokymograms of the left atrium) present this pattern. Therefore, it is logical to assume that the new atrial pattern of pressure is due to transmission of ventricular pressure through the incompetent mitral valve. In the normal heart, no electrokymographic pattern of the posterior border has a plateaulike appearance (confusion with pulsations of the large arteries can be excluded by the appearance in various projections, the different shape and configuration, and the different time relationship[6]). Therefore, a typical plateau can be explained only with the expansion of the left atrial walls due to increased intra-atrial pressure which follows a ventricular pattern when the two chambers communicate through the partly open mitral orifice.

D. *The plateau pattern is significant of stenosis, not of insufficiency.* Supporters of this view base their statements on two data:

1. The experimental tracings of mitral insufficiency published by Wiggers and Feil[35] have been interpreted as tracings of late plateau. Actually, these authors state that "The chief backflow occurs during the phase of systolic ejection and during an interval . . . of 0.08-0.09 into diastole." This corresponds both to our definition of early plateau (see technique) and to the conclusions of an experimental study which proceeded parallel to this clinical study.[38,40] In animals with experimental mitral insufficiency, it may happen that the ECG tracing rises more steeply than the pressure curve of the atrium. This is due to the elasticity of the wall and is unlikely in a severe leak.

2. Tracings of left atrial pressure recorded through the left bronchus, or the back, or obtained at surgery, were said to present more of a plateau pattern

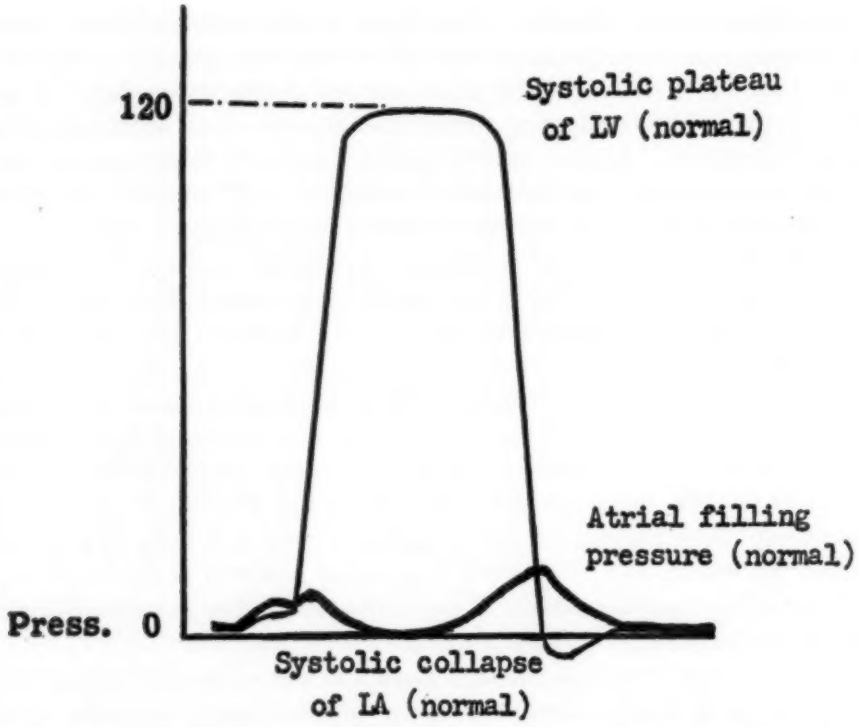

Fig. 6.—Intracardiac pressure patterns of the left ventricle (thin line) and left atrium (thick line) in a normal subject. (Compare with Fig. 2.)

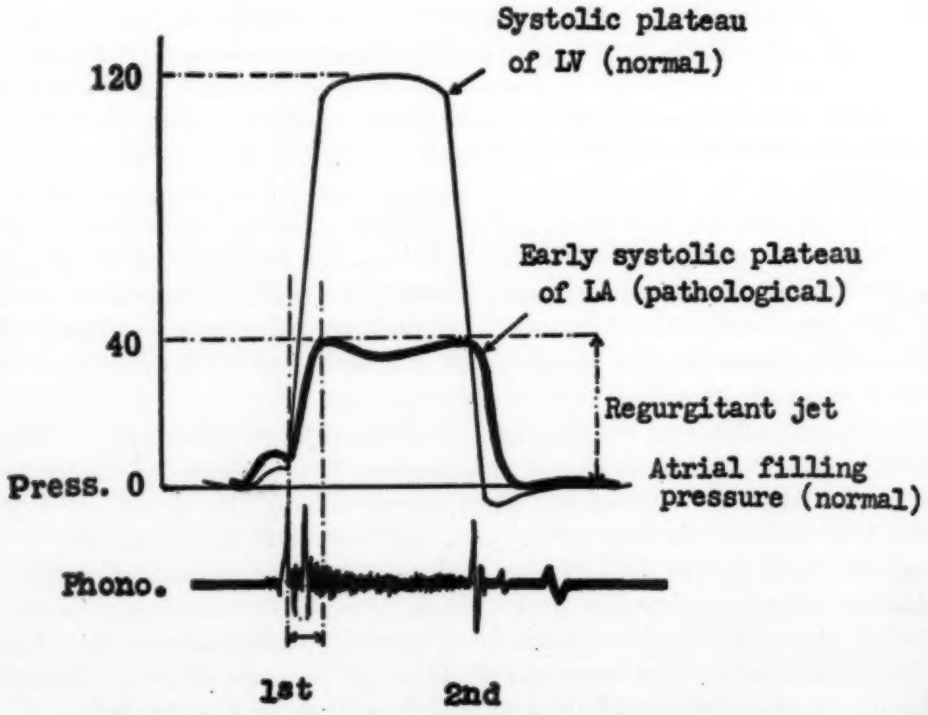

Fig. 7.—Scheme of left ventricular (thin line) and left atrial (thick line) pressures in cases with "pure" mitral insufficiency. There is a systolic plateau in the tracing of ventricular pressure and a systolic plateau (early-plateau) in that of atrial pressure. Atrial filling pressure is normal. (Compare with Figs. 3, 4,*B*, and 5,*B*.)

in pure stenosis than in combined stenosis plus insufficiency.[24-32] Unfortunately, diagnosis of regurgitation by these authors was usually based on either existence of a systolic murmur (which may be faint or even absent if mitral block is also present) or on digital findings by the surgeon (the multiple causes of error of this digital evaluation have been already listed). On the other hand, electrokymograms of cases with pure, or extremely predominant, insufficiency (which was obvious upon surgical or pathologic examination) or following crude valvotomy (in the early stages of surgery, when a leaflet was cut), revealed a tall, typical, and rounded early plateau which was absolutely unmistakable (Fig. 3).

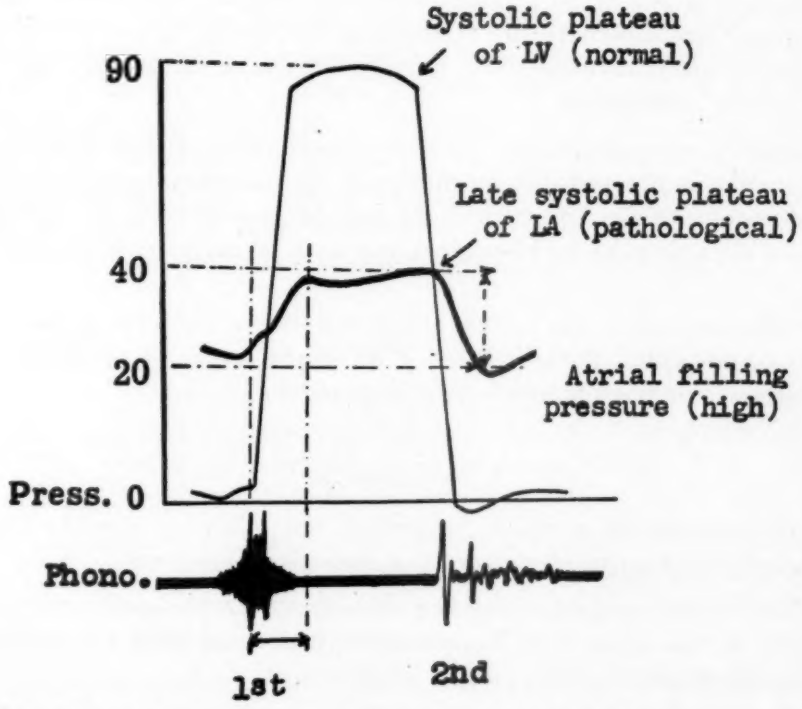

Fig. 8.—Scheme of left ventricular (thin line) and left atrial (thick line) pressures in cases with "pure" mitral stenosis (actually: severe stenosis with moderate insufficiency). There is the normal systolic plateau in the tracing of ventricular pressure and a moderate systolic plateau (late plateau) in that of atrial pressure. This is evidence of moderate regurgitation through a narrow orifice. The atrial filling pressure is high. (Compare with Figs. 4,*A* and 5,*A*.)

For the above considerations, the following conclusions were reached:

a. *Plateau pattern in general:* A plateau pattern is only due to transmission of left ventricular pressure to the left atrial chamber with corresponding distention of its walls. This can be due to either organic lesions of the valve or incompetence caused by a weak myocardium (relative or functional insufficiency). Whenever there is mitral stenosis, the jet is slower because it is opposed by high pressure and occurs through a narrow orifice. It is revealed by a late EKY plateau. If minimal, it may be difficult to record or is observed only in a particularly favorable projection.

b. *Early versus late plateau:* The differentiation between an early and a late plateau was done not only on the basis of theoretic considerations. Tracings similar to those obtained by the EKY of the left atrium in mitral valve defects are obtained by recording a jugular tracing in tricuspid valve defects. In the latter, existence of a late plateau was accepted as evidence of predominant stenosis by Messer and associates[4]; an early plateau, as evidence of predominant insufficiency. This correlation between the two methods in the defects of the two A-V valves was further confirmed by our observation that, whenever surgical commissurotomy relieved the mitral block, the typical late-plateau pattern became that of an early plateau and was observed in more projections. The typical changes of left atrial pressure in mitral defects, recorded by Braunwald and associates[32] are schematically reproduced in Figs. 6, 7, and 8. The coincidence between electrokymographic patterns (Figs. 2, 3, and 4) and pressure patterns is truly remarkable.

c. *Severity of regurgitation:* Exact quantitation of the backflow caused by regurgitation is not possible by means of electrokymography because of the high amplification of the apparatus. It may be grossly done by comparing the above-listed data (one or more projections; late or early plateau) and by calibration.

Electrokymography was recognized of definite value in the gross evaluation of mitral regurgitation, both in cases with severe mitral stenosis and in those without appreciable narrowing of the mitral valve.

DIAGNOSIS

In the diagnosis of valvular deformity, the following considerations were kept in mind whenever an obvious mitral stenosis was present.

1. Electrocardiographic evidence of either left or combined ventricular hypertrophy in the absence of hypertension was considered the result of concomitant severe mitral insufficiency or aortic defect.

2. Phonocardiographic evidence of a loud, all-systolic, apical or midprecordial murmur not transmitted from the base (a diamond-shaped murmur, well recorded at the base, is probably of aortic origin) was considered the result of significant mitral insufficiency. On the other hand, the absence of a significant apical systolic murmur was not considered as excluding mitral insufficiency. Selective phonocardiograms[3] greatly decreased the number of such cases.

3. Phonocardiographic evidence of: (a) marked delay of the first sound over QRS; (b) marked delay of the opening snap over the second sound; and (c) variable length of these intervals in cases of atrial fibrillation were considered evidence of severe mitral stenosis (and vice versa). A loud P_2 indicated high pulmonic diastolic pressure.

4. An early plateau, easily recognized in several projections of the left atrial EKY, was accepted as evidence of severe mitral regurgitation. A late plateau in several projections was accepted as evidence of mitral insufficiency

(probably moderate) associated with the stenosis. A late plateau in only a few projections was considered as evidence of minimal or insignificant insufficiency in the presence of severe stenosis.

5. Correlation of the EKY data with those of the other graphic methods, of the x-ray, and of clinical data has led, in our experience, to a better evaluation of the mitral dysfunction than by any other single method except, possibly, the left atrial pressure tracings.

While two cases revealed evidence of exclusive or extremely predominant insufficiency, no case of stenosis, unaccompanied by some degree of incompetence, was found.

A moderate increase in the amount of blood regurgitating through the mitral orifice did not seem to embarrass the patients, as long as this was obtained by decreasing the severity of mitral stenosis. In other words, the lowering of the left atrial filling pressure was so important that some increase of left atrial pressure during ventricular systole did not decrease its advantage to the patient. As mitral regurgitation is compensated by increased work of the left ventricle, this may be easier to develop than compensation of mitral stenosis with its burden on the pulmonary vessels and the weaker right ventricle.

SUMMARY

Twenty-one patients were studied before and after mitral valve surgery. Nineteen of them had predominant stenosis, and two had predominant insufficiency. The clinical and graphic studies are reported. The comparative value of the various methods is discussed.

General criteria of exclusion from surgery are listed. Coincidence between clinical-graphic diagnosis and surgical evaluation of the valvular lesion was found in the range of about 80 per cent. Possible causes of error in the surgical evaluation of mitral incompetence are discussed.

The electrocardiogram was recognized as a possible guide for evaluating the decrease of right ventricular load and the increase of left ventricular load which may follow surgical intervention.

The phonocardiogram revealed changes of the first sound at the apex and of the second pulmonic sound by effect of surgery. It further revealed a practically constant increase of the interval 2-O.S. and a decrease of the interval R-1 which were considered proportional to the decrease of left atrial pressure. Changes of cardiac murmurs are also described. Phonocardiography was recognized as extremely useful in the diagnosis of mitral stenosis, in the recognition of aortic defects, and in the evaluation of the results of surgery.

Electrokymography was used for the study of left atrial pattern tracings. A typical pattern, entirely different from that of normal subjects, takes place in mitral regurgitation. Possible causes of error are listed. Increased accuracy of study was obtained by taking eight to nine tracings in various projections, by calibrating the tracing, and by analyzing the pattern and its relationship with the heart sounds.

The plateau pattern, previously described by Luisada and Fleischner, was explained by them as the result of mitral regurgitation. While several workers confirmed this interpretation, others raised certain objections. These objections are now refuted in detail.

Two different patterns are now described: the early plateau, significant of exclusive or predominant mitral insufficiency; and the late plateau, revealing predominant mitral stenosis with moderate regurgitation. The atrial and valvular dynamics of the two conditions are analyzed, and it is concluded that the two left atrial electrokymographic patterns are the result of two different left atrial pressure patterns.

The modifications of left atrial pressure by effect of surgery were typically revealed by changes in the electrokymographic patterns.

Correlation of the electrokymographic data with those of other graphic methods, of the x-ray, and of clinical data led to a reliable evaluation of the mitral dysfunction.

While two cases revealed evidence of exclusive or extremely predominant insufficiency, no case of stenosis, unaccompanied by some degree of incompetence, was found.

SUMMARIO IN INTERLINGUA

Vinti-un patientes esseva studiate ante e post operationes del valvula mitral. Es reportate le constatationes clinic insimul con datos phonocardio-, electrokymo-, e electrocardiographic. Le valor comparative del varie methodos es discutite.

Un congruentia de circa 80 pro cento esseva manifeste inter le diagnose clinico-graphic e le evalutation chirurgic del lesiones valvular. Nos discute le possibile fontes de error in le evalutation chirurgic de incompetentia mitral.

Le electrocardiogramma esseva recognoscite como guida possibile in le evalutation del alterationes de carga ventricular que pote sequer le intervention chirurgic.

Le phonocardiogramma revelava un practicamente constante augmento del intervallo 2-OS e un reduction del intervallo Q-1 proportionalmente al reduction del pression sinistro-atrial.

Electrokymographia esseva usate in le studio de registrationes sinistro-atrial. Possibile fontes de error es listate, e nove detalios technic es explicate.

Duo differente configurationes in le electrokymogramma atrial es describite: (1) le plateau de apparition precoce que signala exclusive o predominante insufficientia mitral e (2) le plateau retardate que revela predominante stenosis mitral con regurgitation moderate. Le dynamica atrial e valvular del duo conditiones es analysate, e nos conclude que le duo configurationes sinistro-atrial del electrokymogramma resulta de duo differente configurationes del pression sinistro-atrial.

Le modificationes effectuate per le intervention chirurgic in le pression sinistro-atrial esseva typicamente revelate per alterationes del electrokymogramma.

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THE VECTORCARDIOGRAM IN ANTERIOR MYOCARDIAL INFARCTION. III

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INTRODUCTION

THIS study is a detailed description and analysis of the vectorcardiogram in anterior myocardial infarction. It was undertaken to supplement the morphologic description of the planar vectorcardiogram and to obtain various measurements.

METHODS

Thirty-five patients with a characteristic clinical picture of myocardial infarction were selected for this study. The electrocardiograms in these patients showed the signs customarily considered diagnostic of localized mid-anterior infarction in nineteen, antero-septal infarction in six, and antero-septal plus anterior infarction in four cases.[1-3] In six cases the electrocardiogram was abnormal but not diagnostic, the differential interpretation being between antero-septal infarction and left ventricular hypertrophy or left bundle branch block. These cases were included in this study because their vectorcardiograms displayed features which were similar to those observed in proved cases of anterior myocardial infarction.[4]

Cardiomegaly and/or arterial hypertension was present in twenty-seven cases. Autopsies were performed on four patients and showed localized anterior myocardial infarction.

Horizontal, right sagittal, and frontal planar projections were obtained using the orthogonal reference system of Duchosal with positive polarity. Vectoriographic techniques used in this laboratory are described elsewhere.[5]

The vectorcardiograms were projected on a viewing screen and the magnitude of vectors was measured by dropping perpendiculars from their termini to the horizontal and vertical axes of the screen. The method of analysis has been described in a previous communication.[5] Briefly, the planar projection was arbitrarily divided into initial forces, body, and terminal appendage to facilitate

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description and obtain measurements (Fig. 1). The initial forces are the vectors at the beginning of the loop which are oriented to the right* and/or superior to the null point; they correspond in a general way to q waves in Leads I, V_6, and aV_F. The body comprises those vectors of the QRS loop oriented to the left, inferiorly, anteriorly, and/or posteriorly to the null point. The terminal appendage consists of those vectors at the end of the QRS loop oriented to the right and/or superior to the null point, corresponding in a general way to s waves in Leads I, V_6, and aV_F.

The following observations were noted in the three planar projections of the QRSsÊ loop: angle alpha, which is the angle in the frontal plane subtended by the largest vector of the body or terminal appendage and the horizontal axis; the *long axis* in the horizontal and sagittal planes which is the angle subtended

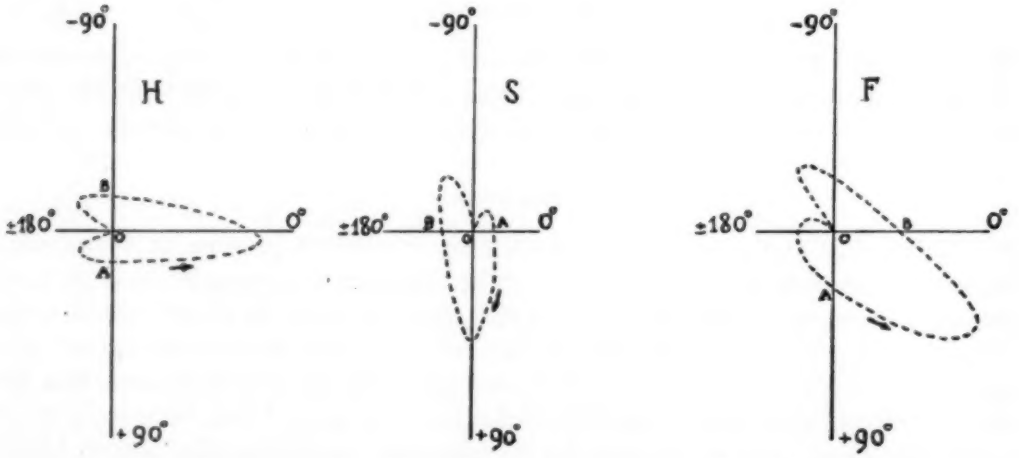


Fig. 1.—Diagrammatic representation of the three planar projections of the QRSsÊ loop defining the position of initial forces, body, and terminal appendage. H = horizontal, S = sagittal, F = frontal plane, in this and subsequent figures. Arrows indicate the direction of inscription of the QRS loop in all figures. OA = initial forces, AB = body, BO = terminal appendage.

by the largest vector of the body and the horizontal axis; the magnitude of the maximal rightward, leftward, anterior, posterior, superior, and inferior vectors of the initial forces, body, and terminal appendage; the magnitude of the maximal anterior-posterior measurement (the width) in the bodies of the horizontal and sagittal plane loops; the maximal rightward-leftward measurement (the width) in the body and terminal appendage of the frontal plane loops; the magnitude of the actual lengths of the largest vector of the initial forces, body, and terminal appendage in the frontal plane; and the duration and direction of inscription of initial forces, body, and terminal appendage in each plane. Other features noted included the position of the S-T junction (J) and the direction of inscription, actual length, position, and angle of the long axes of the T loops in the three planes.

The electrocardiograms were studied in detail.

*Right and left refer to the patient's right and left.

RESULTS*

Horizontal Plane.—The measurements are summarized in Table I.

Initial forces were present in nineteen cases. They were small in both duration and magnitude, and their centrifugal and centripetal limbs were often superimposed. Their direction was variable, being counterclockwise in ten instances and clockwise in nine. These facts contrast to the findings in 100 normal vectorcardiograms in which initial forces are present almost without exception, the centrifugal and centripetal limbs are rarely superimposed, and they are never clockwisely inscribed.[5] In those instances in which initial forces were absent, the earliest vectors were directed to the left and posteriorly in eleven cases and to the left and anteriorly in five.

TABLE I. MEASUREMENTS OF THE HORIZONTAL PLANE QRS LOOP

	PARAMETER	NO. OF CASES	MEAN	RANGE		NORMAL MEAN	RANGE OF NORMAL		MISCELLANY*
				SMALLEST	LARGEST		SMALLEST	LARGEST	
Initial forces	Right	19	0.06 mv.	0.02 mv.	0.20 mv.	0.06 mv.		0.26 mv.	10 cases less than 0.06 mv.
	Anterior	14	0.05 mv.	0.02 mv.	0.08 mv.	0.05 mv.		0.16 mv.	
	Posterior	6	0.03 mv.	0.02 mv.	0.03 mv.				
	Duration	19	0.010 sec.	0.005 sec.	0.020 sec.	0.012 sec.		0.025 sec.	
Body	Left	35	1.07 mv.	0.20 mv.	1.82 mv.	0.86 mv.	.20 mv.	1.65 mv.	
	Anterior	18	0.05 mv.	0.02 mv.	0.12 mv.	0.15 mv.	.03 mv.	0.37 mv.	
	Posterior	35	0.33 mv.	0.06 mv.	1.14 mv.	0.09 mv.		0.25 mv.	19 cases greater than 0.25 mv.
	Width	35	0.21 mv.	0.04 mv.	0.60 mv.	0.15 mv.		0.32 mv.	31 cases less than 0.32 mv.
	Duration	35	0.057 sec.	0.025 sec.	0.093 sec.				
	Angle of the *long axis*†	35	−16.8°	+2°	−60°	+5.87°	+18°	−8°	
Terminal appendage	Right	19	0.26 mv.	0.06 mv.	0.72 mv.	0.12 mv.		0.39 mv.	Only 4 cases greater than 0.39 mv.
	Anterior	3	0.06 mv.	0.02 mv.	0.10 mv.				
	Posterior	16	0.18 mv.	0.02 mv.	0.36 mv.	0.09 mv.		0.25 mv.	
	Duration	19	0.026 sec.	0.008 sec.	0.060 sec.	0.022 sec.		0.045 sec.	Only 2 cases greater than 0.045 sec.
Ratios	Right (I.F.) / Left (Body)	19	0.06	0.03	0.13	0.07		0.21	
	Width (Body) / Left (Body)	35	0.25	0.03	0.78	0.19		0.55	Only 3 cases greater than 0.55
	Right (T.A.) / Left (Body)	19	0.49	0.05	3.60	0.17		0.41	13 cases less than 0.41

mv. = millivolt, sec. = second, I.F. = Initial forces, T.A. = Terminal appendage (Tables 1 to 3).
*Cases of myocardial infarction.
†Values refer to the mean and the range expressed in degrees.

*All measurements of millivolts referred to in the text and tables should be divided by 2 to obtain the actual values recorded on the oscilloscope.

The *long axis* of the body was +2 to −60 degrees, with a mean value of −16.8 degrees; corresponding normal values are +18 to −8 degrees, and 5.87 degrees.[5] The magnitude of the greatest posterior vector ranged from 0.06 to 1.14 millivolt, with a mean of 0.33 millivolt; the corresponding normal values are 0 to 0.25 millivolt, and 0.09 millivolt.[5] Vectors anterior to the null point occurred in eighteen instances, but they were of small magnitude and remained anterior to the null point for only a brief interval. The greatest anterior-posterior measurement (the width) in thirty-one of the thirty-five cases was smaller than the largest value in 100 normal vectorcardiograms. There was no unusual slowness of inscription.

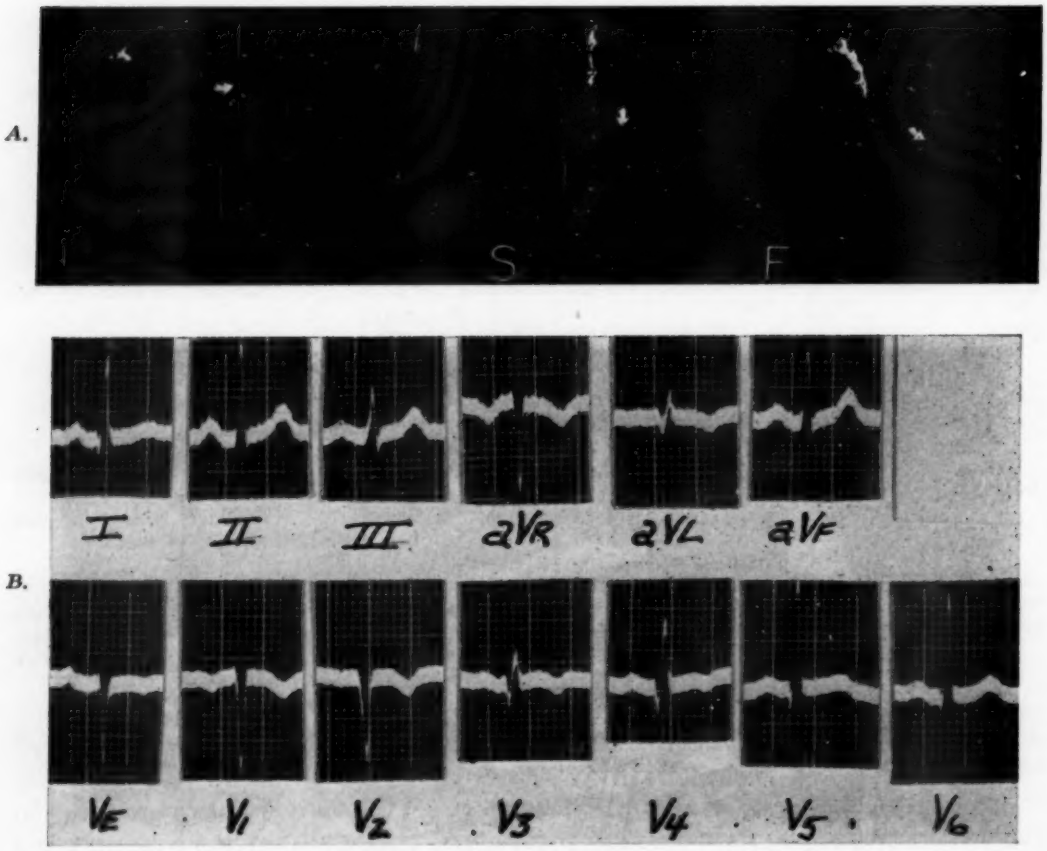


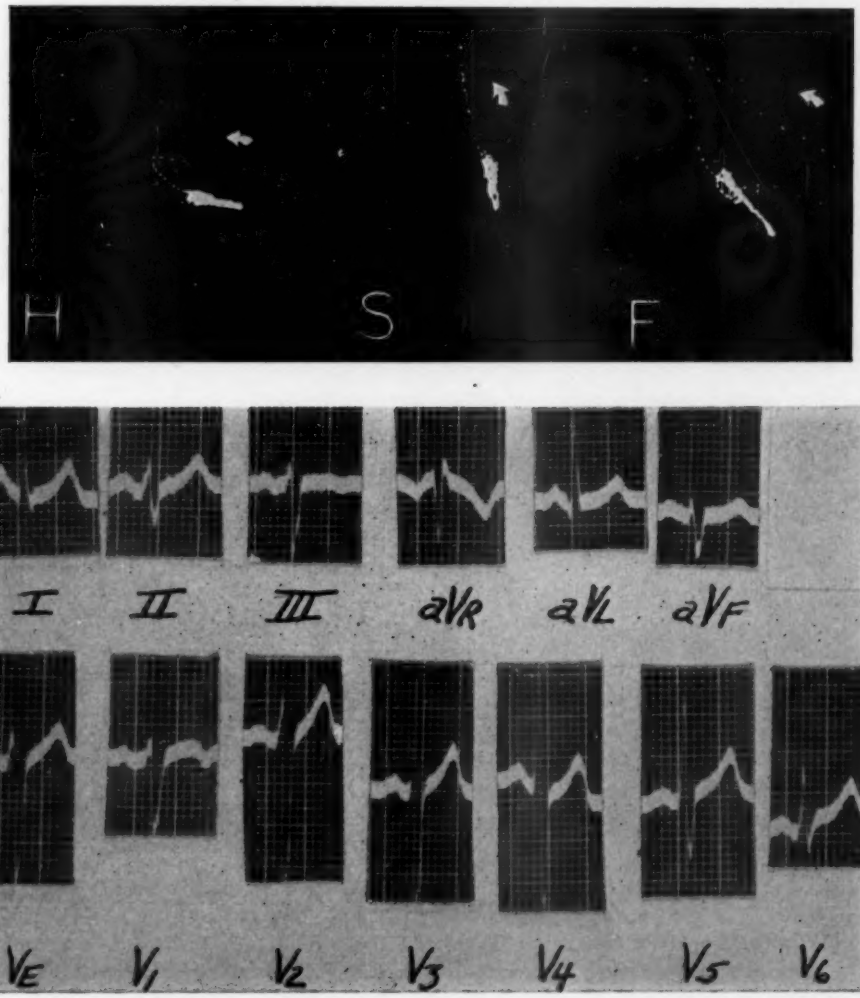
Fig. 2.—*A*, Vectorcardiogram in anterior myocardial infarction. Clockwise inscription of initial forces in horizontal plane. Initial and early vectors are oriented posteriorly. P and T loops not photographed in horizontal plane. *B*, Electrocardiogram from same case as *A*. Signs of anterior infarction in the middle precordial leads.

The most striking morphologic abnormalities were the direction of inscription and contour of the body; noteworthy features were observed in thirty-two of the thirty-five cases.

The loop was inscribed in a counterclockwise direction in twenty-four instances. The initial forces in these were inscribed clockwisely in five (Fig. 2,*A* and *B*) and counterclockwisely in five. In the latter there were sharp indenta-

tions in the centrifugal limb of the loop resulting in concavities facing anteriorly (Figs. 3,*A*, *B*, and 4,*A*, *B*). Eleven of the remaining fourteen cases with counterclockwise inscription of the body did not display initial forces (Fig. 5,*A* and *B*). In three cases the direction of inscription and contour were entirely normal and will be discussed below.

The loop was entirely clockwisely inscribed in five (Fig. 6,*A* and *B*) and partly clockwisely inscribed in six cases. In the latter abrupt shifts in direction posteriorly usually at the proximal portion of the centrifugal limb resulted in crossing of the limbs (Fig. 7,*A* and *B*).



A.

B.

Fig. 3.—*A*, Vectorcardiogram following an attack of chest pain diagnosed as acute myocardial infarction. Morphology and measurements are consistent with left ventricular hypertrophy and are not diagnostic of anterior infarction. *B*, Electrocardiogram from same case as *A*.

These findings contrast sharply to the normal vectorcardiogram and the vectorcardiogram of left ventricular hypertrophy in which counterclockwise inscription of the initial forces and body, and smoothness of contour, without indentations or sudden change in direction, are the rule.[5,6]

Terminal appendages were present in nineteen cases, and were oriented to the right and posteriorly. They were small in the majority of instances. In several, however, they were large, and were associated with small bodies that were posteriorly displaced.

Sagittal Plane.—The measurements are summarized in Table II.

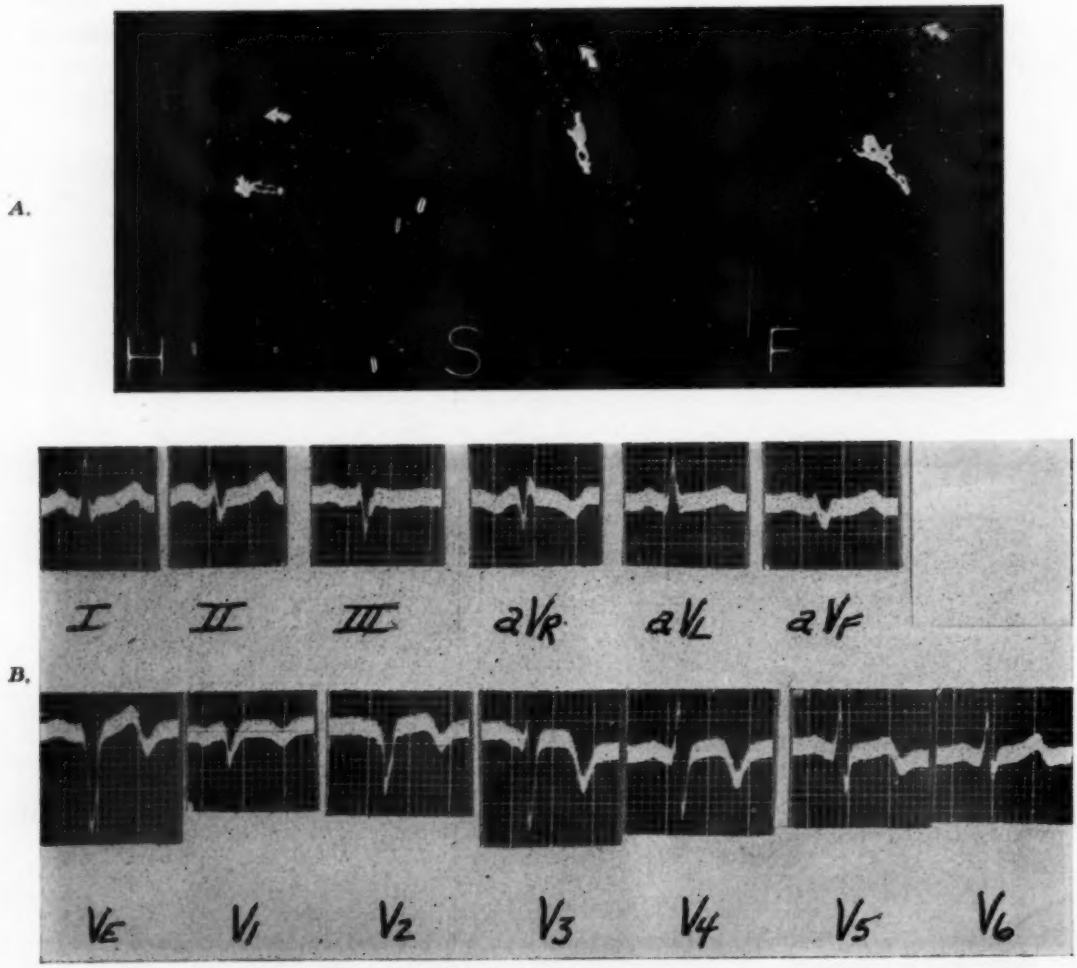


Fig. 4.—*A*, Vectorcardiogram obtained 27 days after that in Fig. 3, *A*. Sudden change in direction to a posterior orientation of the centrifugal limb in the horizontal plane, resulting in a concavity facing anteriorly. *B*, Electrocardiogram from same case as *A*. Signs of anteroseptal infarction.

Initial forces were present in ten cases; they were short in duration and small in magnitude, and were counterclockwisely inscribed or superimposed on each other in eight instances. Initial forces occur in the large majority of normal vectorcardiograms and are always clockwisely inscribed.[5] Among the twenty-five cases with no initial forces the earliest vectors were directed slightly anteriorly and inferiorly in sixteen, and posteriorly and inferiorly in nine. These vectors are never posteriorly directed in normal vectorcardiograms.

As in the horizontal plane the measurements of the *long axis* and the magnitude of the greatest posterior vector (Table II) indicate posterior displacement of the body of the QRS loop. The magnitude of the greatest inferior vector of the body was generally small, i.e., smaller than in the normal[5] (Table II). Similar observations have been noted in uncomplicated left ventricular hypertrophy,[6] in which the length of the body is often considerably smaller than the length of the superiorly directed terminal appendage.

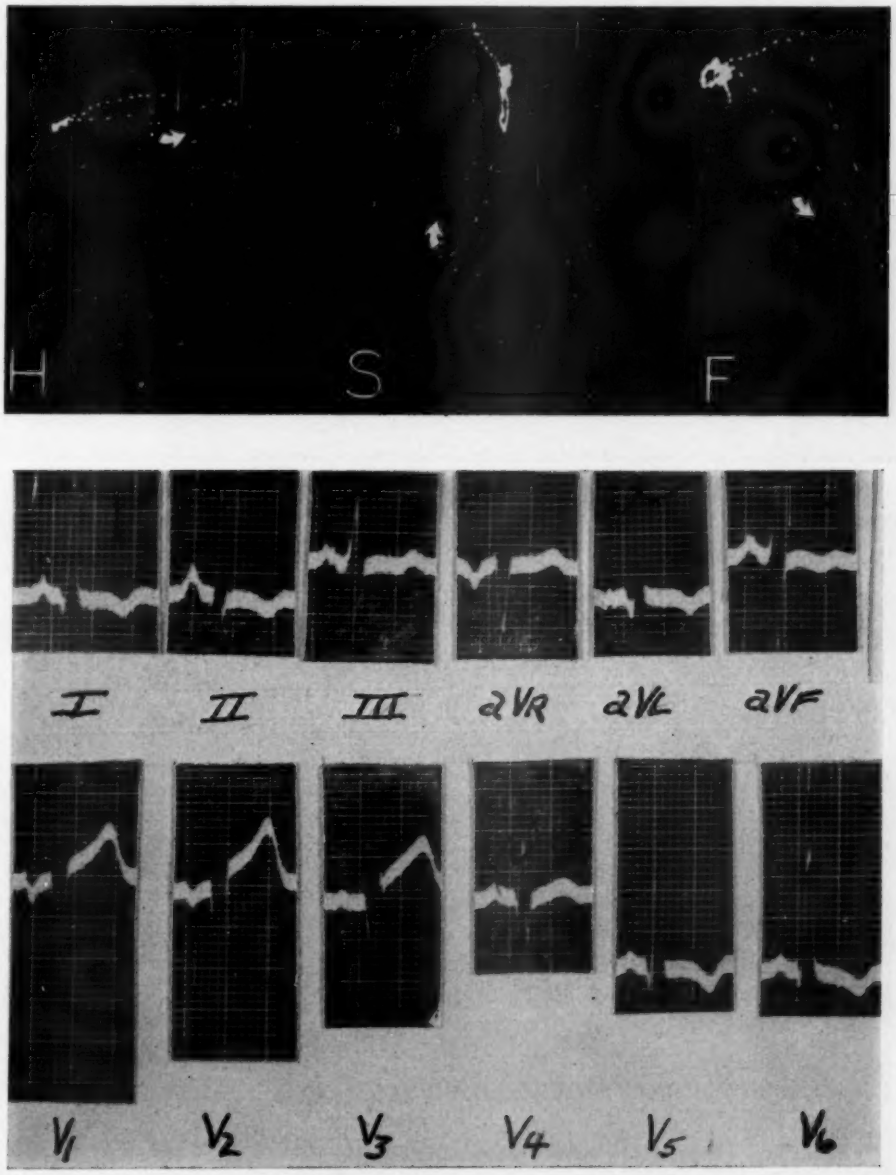


Fig. 5.—*A*, Vectorcardiogram in anterior myocardial infarction. Initial forces absent, and earliest vectors are directed to the left and posteriorly in horizontal plane. P and T loops not photographed in horizontal plane. *B*, Electrocardiogram from same case as *A*. Signs of anteroseptal infarction.

The duration of the body was not prolonged. The direction of inscription of the body was clockwise in thirty-three, and partly counterclockwise in two cases. Abrupt changes in direction posteriorly resulted in crossing of the limbs in two cases and concavities facing anteriorly and inferiorly in ten. Clockwise inscription of the body is invariable in normals and sudden shifts in direction do not occur.[5]

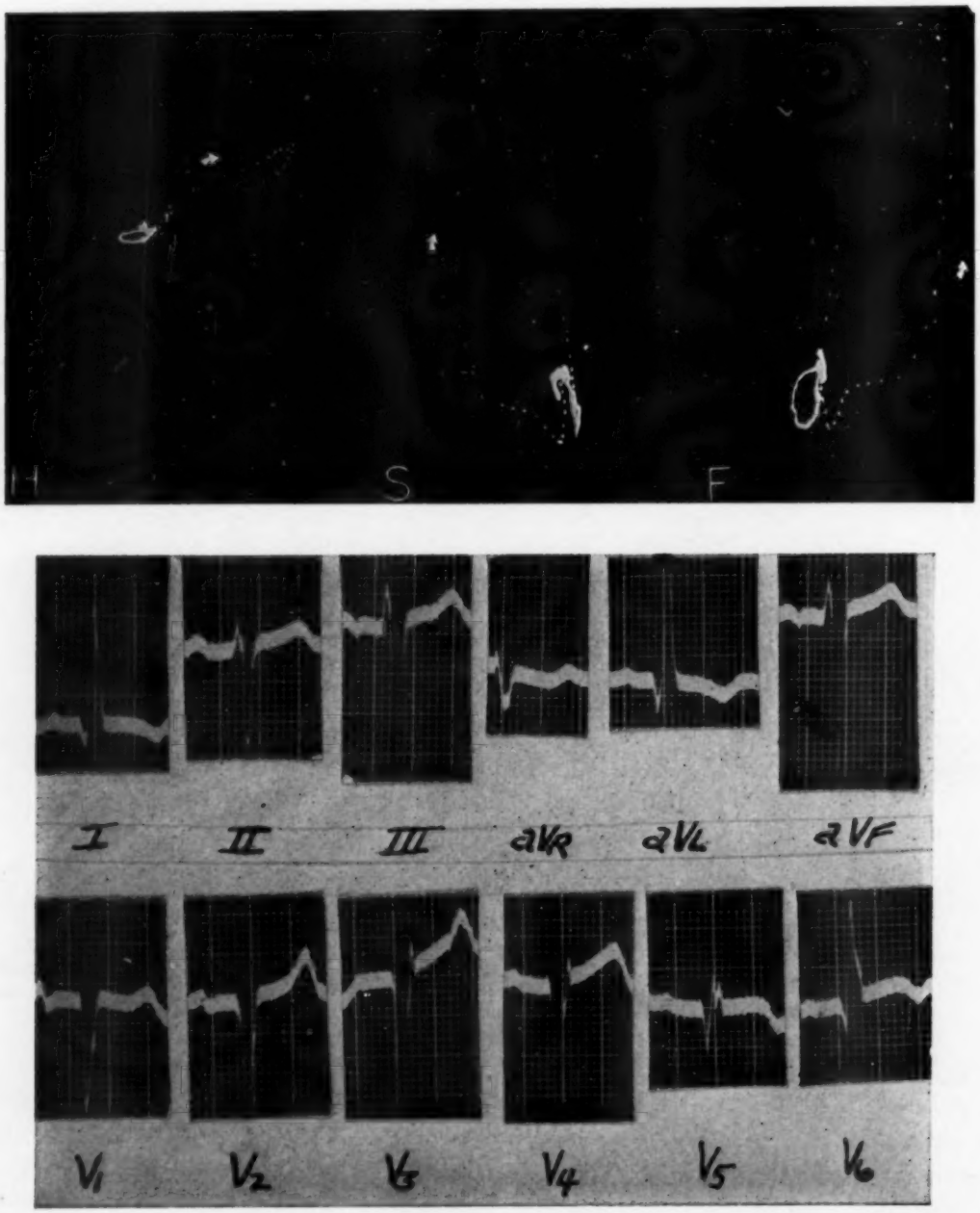
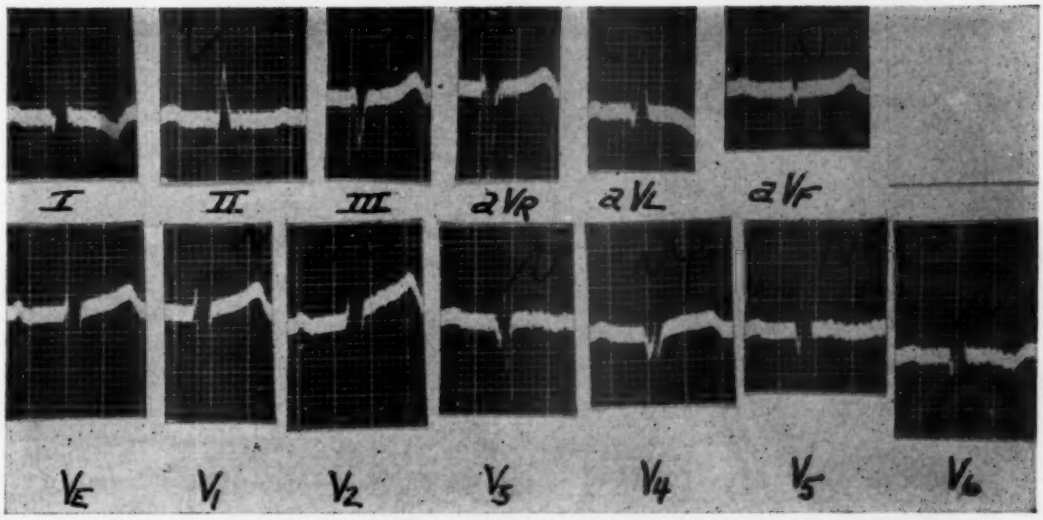


Fig. 6.—*A*, Vectorcardiogram in anterior myocardial infarction. Clockwise inscription of entire horizontal plane QRS loop. *B*, Electrocardiogram from same case as *A*. Signs of extensive anterior infarction.

A terminal appendage was present in twenty-six of the thirty-five cases and was often large. There was considerable variation in the magnitude of the maximal superior vector. The greatest posterior vector was large in many cases (Table II), indicating posterior orientation of the terminal forces. The ratio of the maximal superior forces of the terminal appendage to the maximal inferior forces of the body varied within wide limits and was often greater than unity. The latter feature does not occur in the normal vectorcardiogram,[5] but is common in uncomplicated left ventricular hypertrophy.[6] The appendage was inscribed in the same direction as the body except in three cases; it was rapidly traced as a rule, its contour was smooth, and did not display sudden changes in direction.

A.



B.

Fig. 7.—*A*, Vectorcardiogram in anterior myocardial infarction. Posterior orientation of the centrifugal limb and crossing of the limbs in the horizontal plane QRS loop. P and T loops not photographed in horizontal plane. *B*, Electrocardiogram from same case as *A*. Signs of mid-anterior infarction.

Frontal Plane.—The measurements are summarized in Table III.

Initial forces were present in twenty-two cases. They were directed to the right in twenty-one and were small in magnitude and of short duration. The initial forces were oriented inferiorly in thirteen instances. In ten of these the trace quickly reversed its direction and crossed the null point. At the instant of

crossing the magnitude of the vector was 0.14 millivolt or less. On the other hand, in the three remaining cases, this measurement was 0.56, 0.70, and 0.90, respectively (Fig. 8,*A* and *B*). The corresponding measurement in the normal vectorcardiogram varies between 0.08 and 0.32 with a mean of 0.17 millivolt.[5]

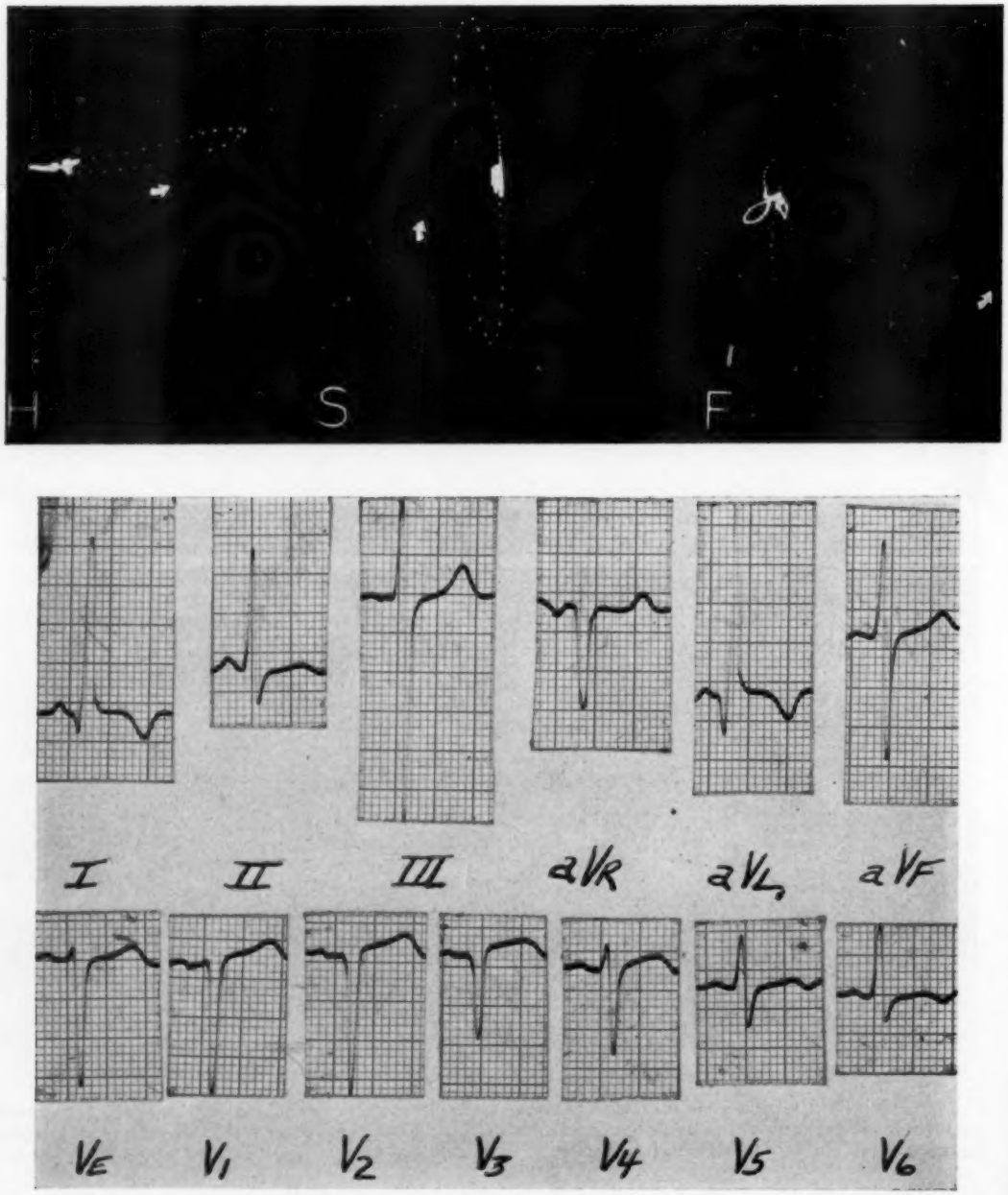


Fig. 8.—*A*, Vectorcardiogram in anterior myocardial infarction. Initial forces in the frontal plane oriented slightly to the right and inferiorly, and are unusually large. No diagnostic signs of infarction in horizontal plane QRS loop. *B*, Electrocardiogram from same case as *A*. Signs of anterior infarction in Leads *I*, aV_L, V_2, and V_3. Leads V_E, V_1, V_2, and V_3 at one-half normal standardization.

TABLE II. MEASUREMENTS OF THE SAGITTAL PLANE QRS LOOP

	PARAMETER	NO. OF CASES	MEAN	RANGE		NORMAL MEAN	RANGE OF NORMAL		MISCELLANY*
				SMALLEST	LARGEST		SMALLEST	LARGEST	
Initial forces	Anterior	4	0.02 mv.	0.02 mv.	0.03 mv.	0.05 mv.		0.16 mv.	
	Posterior	4	0.04 mv.	0.03 mv.	0.05 mv.				
	Superior	10	0.05 mv.	0.03 mv.	0.08 mv.	0.08 mv.		0.37 mv.	
	Duration	10	0.008 sec.	0.006 sec.	0.010 sec.	0.013 sec.		0.025 sec.	
Body	Inferior	35	0.86 mv.	0.03 mv.	2.72 mv.	1.53 mv.	0.32 mv.	3.03 mv.	
	Anterior	20	0.07 mv.	0.02 mv.	0.24 mv.	0.10 mv.	0.02 mv.	0.26 mv.	12 cases less than 0.07 mv.
	Posterior	35	0.28 mv.	0.03 mv.	1.00 mv.	0.09 mv.	0.02 mv.	0.32 mv.	
	Width	35	0.26 mv.	0.03 mv.	1.06 mv.	0.15 mv.	0.03 mv.	0.32 mv.	
	Duration	35	0.044 sec.	0.008 sec.	0.105 sec.				
	Angle of the *long axis*†	35	+101°	+80°	+160°	+89.72°	+85°	+97°	
Terminal appendage	Anterior	5	0.09 mv.	0.01 mv.	0.19 mv.				
	Posterior	26	0.35 mv.	0.08 mv.	0.90 mv.	0.10 mv.		0.27 mv.	
	Superior	26	0.53 mv.	0.06 mv.	2.42 mv.	0.23 mv.		0.53 mv.	
	Duration	26	0.035 sec.	0.009 sec.	0.093 sec.	0.028 sec.		0.045 sec.	
Ratios	Superior (I.F.) / Inferior (Body)	10	0.04	0.02	0.06	0.05	0.01	0.17	
	Width (Body) / Inferior (Body)	35	0.63	0.04	3.20	0.11	0.02	0.54	
	Superior (T.A.) / Inferior (Body)	26	1.90	0.03	6.60	0.20	0.03	0.43	

*See footnote, Table I.
†See footnote, Table I.

The initial forces were superiorly directed in ten cases. As in the sagittal plane, they were small in magnitude and of short duration. In four instances they were inscribed clockwisely and their centrifugal and centripetal limbs were close to one another, as in the normal vectorcardiogram.[5]

The initial forces were counterclockwisely inscribed in eighteen cases.

The eariliest vectors were directed to the left and inferiorly in the thirteen cases without initial forces, a feature rarely observed in the normal vectorcardiogram.[5]

The QRS loop tended to be horizontally placed. The mean value for angle alpha was 4.9 degrees, compared to the normal of 65.69 degrees.[5] The actual length of the body, and the largest inferior vector were normally small but variable. However, as noted for the sagittal plane, the superior potentials in the terminal appendage were large. The maximal rightward to leftward measurement (width) of the body was considerably greater than in the normal vectorcardiogram.[5] The direction of inscription of the body was counterclockwise in

twenty-six, and clockwise in nine vectorcardiograms. The duration of the body was not greater than normal. Similar observations have been noted in uncomplicated left ventricular hypertrophy; horizontal position, small body, large terminal appendage oriented to the left and superiorly, excessive width of the body, and counterclockwise inscription.[6] However, in fourteen cases with counterclockwise inscription of the body there were sudden changes in direction of the early forces resulting in indentations of the trace, corresponding to similar irregularities of contour in the other two planes. The latter abnormality is not found in uncomplicated left ventricular hypertrophy.[6]

TABLE III. MEASUREMENTS OF THE FRONTAL PLANE QRS LOOP

	PARAMETER	NO. OF CASES	MEAN	RANGE		NORMAL MEAN	RANGE OF NORMAL		MISCELLANY*
				SMALLEST	LARGEST		SMALLEST	LARGEST	
Initial forces	Right	21	0.05 mv.	0.03 mv.	0.20 mv.	0.06 mv.		0.28 mv.	
	Left	4	0.04 mv.	0.03 mv.	0.05 mv.				
	Superior	10	0.07 mv.	0.03 mv.	0.12 mv.	0.08 mv.		0.40 mv.	
	Inferior	13	0.22 mv.	0.04 mv.	0.95 mv.	0.17 mv.	0.08 mv.	0.32 mv.	10 cases 0.14 mv. or less
	Duration	22	0.018 sec.	0.005 sec.	0.023 sec.	0.016 sec.		0.028 sec.	
Body	Left	35	1.03 mv.	0.24 mv.	1.74 mv.	0.78 mv.	0.21 mv.	1.63 mv.	
	Inferior	35	0.87 mv.	0.14 mv.	2.80 mv.	1.52 mv.	0.26 mv.	2.81 mv.	
	Width	35	0.68 mv.	0.06 mv.	1.68 mv.	0.24 mv.	0.05 mv.	0.60 mv.	
	Length (actual)	35	1.33 mv.	0.18 mv.	2.92 mv.	1.67 mv.	0.63 mv.	3.16 mv.	
	Duration	35	0.042 sec.	0.018 sec.	0.064 sec.				
	Angle α†	35	+4.9°	+67°	−116°	+65.69°	+80°	+23°	
Terminal append-age	Right	23	0.23 mv.	0.04 mv.	0.64 mv.	0.12 mv.		0.40 mv.	
	Left	22	0.93 mv.	0.08 mv.	2.49 mv.				
	Superior	28	0.53 mv.	0.06 mv.	2.44 mv.	0.23 mv.		0.53 mv.	
	Inferior	7	0.29 mv.	0.03 mv.	0.93 mv.				
	Width	31	0.53 mv.	0.04 mv.	1.94 mv.	0.17 mv.		0.57 mv.	
	Length (actual)	31	0.93 mv.	0.08 mv.	2.50 mv.	0.26 mv.		0.58 mv.	
	Duration	31	0.037 sec.	0.008 sec.	0.095 sec.	0.027 sec.		0.045 sec.	
Ratios	Width (Body) / Length (Body)	35	0.62	0.04	1.11	0.16	0.03	0.68	
	Length (T.A.) / Length (Body)	31	1.18	0.05	5.40	0.20		0.70	

*See footnote, Table I.

†See footnote, Table I.

A terminal appendage was present in thirty-one cases. The superiorly directed vectors of the appendage were large and their sweep wide and smooth in contour, resulting in a large right-to-left measurement (width). The direction of inscription was counterclockwise in twenty-four cases. Unusual slowness of inscription of the terminal appendage was not observed. These features resemble those noted in uncomplicated left ventricular hypertrophy.[6]

S-T Junction (J) and TsÊ Loop.—The QRSsÊ loop was open in twenty-seven cases, closed in five, and could not be determined in three. The S-T junction was always oriented to the right. It was located anteriorly and either superiorly or inferiorly in fifteen cases, and posteriorly and superiorly in seven. In the remaining five cases it was located to the right without displacement in the sagittal and vertical axes.

The T loop in the horizontal plane was small and oriented markedly to the right of and slightly anterior to the QRS loop; it subtended an angle with the long axis between 160 and 180 degrees. The QRS-T angle was usually close to 180 degrees. This orientation of the T loop and the large QRS-T angle are strikingly different from the normal vectorcardiogram in which the long axes of the QRS and T loops are separated by a few degrees only.[5] The direction of inscription of the T loop was counterclockwise in twenty cases, clockwise in nine, and could not be determined in six. The directions of inscription of the QRS and T loop were opposite one another in seven instances. In the normal vectorcardiogram the directions of inscription of the QRS and T loops are always the same in the horizontal and sagittal planes; counterclockwise in the former and clockwise in the latter.[5]

The T loop in the sagittal plane was small and oriented anteriorly and inferiorly, i.e., between 70 and 90 degrees. The size of the QRS-T angle varied considerably, but was generally much smaller than in the horizontal plane. The direction of inscription was clockwise in twenty, and could not be determined in the remaining cases. Directions of inscription of the QRS and T loops were opposite in only one case.

The T loop in the frontal plane was small and round, and oriented to the right and inferiorly, or to the right and superiorly, i.e., between +90 and −90 degrees. The QRS-T angle was approximately 180 degrees. Directions of inscription of the QRS and T loops were concordant in twenty cases, and discordant in eleven. The direction of inscription of the T loop was counterclockwise in twenty-four cases, and clockwise in seven.

The Electrocardiogram.—A summary of the electrocardiographic observations is presented in Table IV. In Lead I, q waves were observed in twenty cases and initial r or R waves in twenty-nine in Lead II and twenty-eight in Lead III. In Lead III, rS deflections were present in eighteen instances. Lead aV_R disclosed initial q or Q waves in fourteen, QS deflections in eleven, and initial r waves in ten cases. An rSr′ complex in Lead aV_R occurred once. Lead aV_L was similar to Lead I, with twenty-two cases disclosing q or Q waves. Initial r or R deflections in Lead aV_F were present in twenty-five cases.

In the unipolar precordial leads q or QS deflections (usually the latter) were present in Lead V_E in ten cases, in Lead V_{3R} in sixteen, in Lead V_1 in eighteen, in Lead V_2 in twenty-one and in Lead V_3 in twenty. In Leads V_4, V_5, and V_6 q waves were present in twelve, thirteen, and fourteen instances, respectively. In V_4, QS deflections were noted in three tracings. Diminishing height of initial r waves as the electrode was moved from V_{3R} to V_3 was the only QRS abnormality noted in one case.

TABLE IV. TYPE OF QRS COMPLEX NOTED IN THE 14-LEAD ELECTROCARDIOGRAM

	I	II	III	aV_R	aV_L	aV_F	V_E*	V_{3R}†	V_1	V_2	V_3	V_4	V_5	V_6
qR	18	5	3	2	17	5				1		1	10	12
qRs	1	1	2	1		3	1				2	4	2	2
qrs					2							1		
qr				6				1						
qrS	1					1	2			1	2			
qs						1								
QR			1								2	3		
QRS										1		1		
QRs												1		
QS				11	1		6	15	17	16	11	3		
Qr				5	2				1	2	3	1	1	
Qrs			1				1							
rS	2	5	18	9	2	12	15	18	14	13	14	9	4	3
rs	4	3			1	5								
rsr′			1		1								1	1
rSr′		1	1	1	1				3					1
r					1									
rsRs′												1		
rsr′s′												1		
Rs	2	11	2		2	3						3	7	8
RS		3	2		1	2				1	1	4	4	1
R	7	6	4		4	3						2	6	7

Numerals refer to the number of cases.
*This lead not obtained in 10 cases.
†This lead not obtained in 1 case.

S-T segment elevations were often present in the right and midprecordial leads early in the course of an acute myocardial infarction followed later by plane coved inverted T waves. On the other hand the limb leads rarely disclosed significant S-T segment abnormalities, although T wave changes were often noted.

The mean QRS interval was 0.081 second, with a range from 0.06 to 0.12 second. Only eight of the thirty-five cases had QRS intervals 0.10 second or greater.

DISCUSSION

At each instant during cardiac systole all electrical forces summate into one manifest force having magnitude, direction, and sense.[7,8] The manifest force is called the cardiac vector and the projection of its terminus in the horizontal, sagittal, and frontal planes from instant to instant throughout systole traces the vectorcardiographic loop.[8] When myocardial infarction occurs, or when myocardial fibers become unresponsive as a result of sublethal injury, the involved fibers are rendered electrically inert, and there is a new balance of forces directed away from the inert area.[4,8,9] Although these changes may take place throughout the entire period of ventricular depolarization, modification of the early, less complex part of the curve is probably greater and more easily recognized than alterations occurring later.[4]

Therefore, since the abnormal initial and early forces point away from an inert area, it may be assumed that they would be oriented posteriorly and infer-

iorly in anterior wall infarction.[4] This assumption is substantiated by the observations reported in this study.

The most striking changes occur in the horizontal planar projection which records the anterior-posterior and right-left components of the cardiac vector. There is an abnormal orientation of the initial and/or early forces in a posterior direction. This is expressed by a variety of features which are of diagnostic value: small initial forces which are clockwisely instead of counterclockwisely inscribed, absence of initial forces with orientation of the earliest vectors to the left and posteriorly, and abrupt changes in direction posteriorly in the early part of the centrifugal limb of the body resulting in concavities facing anteriorly, or more often, clockwise inscription of the loop or crossing of the centrifugal and centripetal limbs. These abnormalities of contour are not observed in left ventricular hypertroply.[6]

Although the long axis and the magnitude of the greatest posterior vector in the horizontal plane are not dissimilar from corresponding values in left ventricular hypertrophy, the loop in infarction is much narrower in the anterior-posterior axis (width); this is probably the result of the loss of anterior forces in myocardial infarction, which, of course, does not occur in uncomplicated ventricular hypertrophy.

The corresponding abnormal posterior orientation of the resultant vectors is noted in the sagittal planar projection which records the anterior-posterior and superior-inferior components of the heart vector. Although the loss of anterior potential and augmentation of posterior potential is not as apparent in the sagittal as in the horizontal plane, careful analysis of the early forces disclose several features of diagnostic value, i.e., abrupt changes in direction that occur frequently and result in irregularity of contour and, in several instances, crossing of the limbs.

There are, as noted earlier, forces of considerable potential in the mid- and terminal portions which are not readily distinguished from those occurring in left ventricular hypertrophy.[6] It is of interest, therefore, that the great majority of cases in this study had left chamber enlargement. Since, by the method of selection, these are cases of anterior wall infarction, hypertrophy, if it occurs, must principally involve the uninfarcted muscle fibers of the lateral and posterior walls. This has the same effect on the mid- and late over-all cardiac vectors as anterior infarction itself, namely, augmentation of the electrical forces in a posterior and superior direction away from the electrically inert area of the anterior wall. Therefore, although the multiplicity of factors in the middle and later portions of ventricular systole make it difficult to distinguish between myocardial infarction and uncomplicated left ventricular hypertrophy, abnormalities of the initial and early forces allow this differentiation to be made.

Similarly, in the frontal planar projection, which records the right-left and superior-inferior components of the heart vector, there are irregularities of contour in the early forces which correspond to the similar abnormalities observed in the other planar projections and which are not observed in left ventricular hypertrophy.[6] The trace in the mid- and later portions of ventricular systole cannot be differentiated from left ventricular hypertrophy.[6]

In three instances in which the initial forces in the frontal plane are oriented slightly to the right and inferiorly, they attain an abnormally large magnitude before crossing the null point. This feature was never observed in left ventricular hypertrophy.[6] Moreover, since the magnitude of the rightward component was not abnormal, lateral wall infarction was excluded.[6,9] The right and inferior orientation of the abnormal vectors suggests localized infarction high in the mid-anterior or high anteroseptal wall of the left ventricle. Nevertheless, it is interesting that the horizontal loops did not disclose diagnostic signs of anterior infarct in these three cases.

Slow inscription of the QRS loop does not occur or is not characteristic. Evidently, intraventricular or peri-infarction block is not a common feature of anterior myocardial infarction. This is also indicated by the rarity of prolongation of the QRS interval in the electrocardiogram.

The position of the S-T junction (J) is characteristic. It is always oriented to the right. However, there is variability in the superior-inferior and anterior-posterior axes. Ventricular hypertrophy and digitalis therapy undoubtedly influence its orientation.

The orientation of the T loop and its direction of inscription has diagnostic value. The T loop in most cases is located considerably to the right of, inferiorly, and slightly anteriorly to the QRSs$\hat{E}$ loop. It has a similar orientation in left ventricular hypertrophy and left bundle branch block. However, in the two latter conditions the direction of inscription of the T loop is usually the same as in the body.[6] In many of the cases of infarction the direction of inscription of the T loop is opposite that of the body and is a sign of myocardial ischemia.

These observations reveal that the vectrocardiographic diagnosis of anteroseptal and mid-anterior myocardial infarction is most clearly indicated by specific abnormalities of orientation of the initial and early vectors in the horizontal plane loop. These abnormalities, of course, also produce diagnostic changes in the corresponding portions of the sagittal and frontal plane loops, which, however, are not helpful in localization. Furthermore, these signs furnish important evidence useful in the differential diagnosis of left ventricular hypertrophy and myocardial infarction.

SUMMARY

1. The planar vectorcardiograms obtained from thirty-five patients with anteroseptal and/or localized mid-anterior myocardial infarction were described and measurements of the QRS and T loops were made.

2. Anterior wall infarction results in a new orientation of the initial and early vectors of the QRSs$\hat{E}$ loop in a posterior and inferior direction. This new orientation produces characteristic abnormalities which are clearly evident in the horizontal planar projection.

3. Although the general morphology and measurement of the sagittal and frontal planar projections suggest left ventricular hypertrophy, the irregularities of contour in the early part of the loop corresponding to those mentioned in (2) make possible the differentiation between left ventricular hypertrophy and anterior myocardial infarction. In addition, these several features

permit the combined diagnosis of left ventricular hypertrophy and anterior myocardial infarction to be made.

4. Diagnostic features in the horizontal plane loops were present in all but three of thirty-five cases. However, the frontal plane loops in the exceptions disclosed abnormally large initial vectors diagnostic of localized infarction high on the anteroseptal or anterior wall.

5. The S-T junction (J) is always oriented to the right and, usually, anteriorly. The TsÊ loop is oriented to the extreme right, slightly anteriorly, and inferiorly; and is often inscribed in a direction opposite to the QRS sÊ loop.

SUMMARIO IN INTERLINGUA

Es describite vectocardiogrammas planar obtenite abtrenta-cinque patientes con infarcimento myocardial anterior. Mesurationes del ansas QRS e T es presentate. Le constatationes indica que le infarcimento del pariete anterior resulta pro le vectores initial e precoce del ansa QRSsÊ in un nove orientation postero-inferior que produce anormalitates characteristic. Iste anormalitates es le plus clarmente obvie in le projection planar horizontal. Aspectos del tres projectiones planar es describite que rende possibile le differentiation inter le vectocardiogrammas in infarcimento anterior e in hypertrophia sinistro-ventricular.

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CANCELLATION OF THE ABNORMAL QRS COMPLEX OF HEART DISEASE

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IN THE past, it was accepted widely[1,2] that an electrocardiographic QRS pattern recorded from a precordial electrode was derived predominantly from a localized current source in the immediately subadjacent heart muscle. This assumption is contradicted by Schmitt's[3] and Frank's[4] experimental observations in human subjects that the same QRS pattern, reversed in polarity, may be recorded from two electrodes, one on the precordium and one elsewhere on the body, each paired with the same reference terminal. If it were true that the potential recorded from a precordial electrode were derived locally, it would be difficult to explain the derivation of the same signal, reversed in polarity, recorded from the remote site.

On the other hand, the occurrence of mirror images, as these paired patterns have been called, is to be expected if one postulates that electrical activity of the heart can be represented by a single fixed-location equivalent dipole.[3,4] Accordingly, Schmitt and his associates[3] searched for mirror patterns in a series of thirty-four patients and seventeen normal subjects, in order to evaluate the applicability of the equivalent dipole hypothesis to patients. They used a Wilson central terminal for all pairings. The difference in shape between signals of each pair was measured by a quantitative cancellation technique. They found the residual (or noncancelling signal) to be small in a high percentage of the normal subjects, and in a lesser proportion of the patients. They reported that patients with certain kinds of electrocardiographic abnormality, such as bundle branch block and "ventricular strain" often exhibited very poor cancellation. They concluded that the fixed-location equivalent dipole hypothesis was applicable for most normal subjects and many patients.

Frank,[4] using a four-electrode cancellation technique, studied a single normal individual in great detail, and concluded that ventricular depolarization could be represented in his subject by a single equivalent dipole with an accuracy of 95 per cent. Furthermore, he demonstrated the fallacy of Schmitt's belief that the phenomenon of cancellation depended upon the use of a reference terminal approximating the electrical center of the heart, and demonstrated that the position of the remote electrode of the cancelling pair could be predicted from a study of the distribution of the electrical field derived from a properly located dipole in a torso model.

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We have been interested in the development of vectorcardiography on a sound, quantitative physical basis. Since the fundamental cornerstone of vectorcardiography is no firmer than the degree of validity of the equivalent dipole hypothesis—a hypothesis which is not yet firmly established for patients—we undertook to determine, in the patients, the degree to which ventricular depolarization could be represented by a single dipole. In this study, most of the patients were specially selected ones with specifically abnormal complexes confined in standard precordial leads to local areas of the precordium which, in the past, would have been attributed to proximal myocardial current generators and, hence, considered unexplainable by dipole behavior.

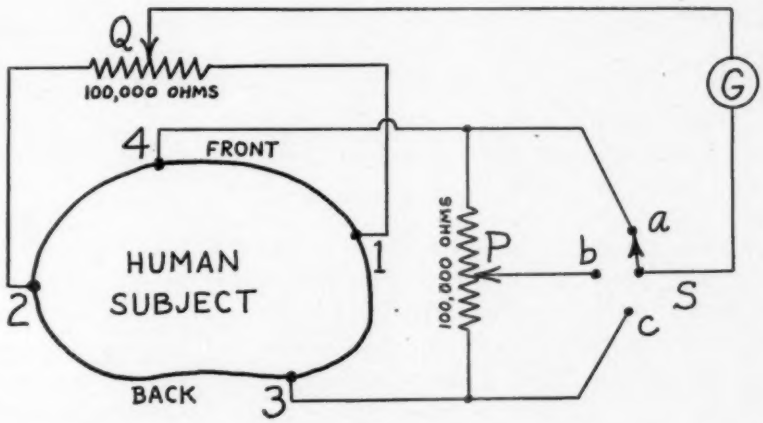

Fig. 1.—With switch *S* in the "*a*" position, the pattern at electrode *4* is examined with respect to terminal *Q*. When switch *S* is in position "*c*", the mirror pattern at electrode *3* is examined, with respect to *Q*. Finally, with switch *S* in the "*b*" position, a null is recorded, comprised of the measured residual voltage between *P* and *Q*. *G* represents a preamplifier feeding a Viso-Cardiette.

The four-electrode concellation technique of Frank was used as a criterion to test the dipolar nature of the abnormal QRS complexes. Mirror patterns were sought at sites remote from the precordium. The degree of cancellation represented the degree to which the abnormal QRS complex could be explained by the action of a single equivalent dipole. Of the sixty-two patients studied, all showed mirror patterns of "local" precordial complexes, with cancellation of 80 per cent or better.

METHOD

Sixty-two patients were studied with the four-electrode cancellation technique of Frank schematically illustrated in Fig. 1. Electrodes 1 and 2 were placed on the anterolateral chest walls at the approximate mid-heart level and were connected with a resistor with sliding tap Q, the reference terminal. Electrode 4 was placed on the precordium at the site of the locally bizarre recording in standard electrocardiography, if such a pattern were found. It was connected through a resistor to electrode 3. The pattern Q versus 4 was then recorded,

with Q at an arbitrarily fixed position along the resistor. Guided by data derived from torso models, geometrically portrayed in image surface diagrams,[5] electrode 3 was placed on the chest at a position likely to yield a mirror image of the pattern Q versus 4. The 3 versus Q pattern was then recorded. Further recordings were made after each small change in the location of electrode 3 until

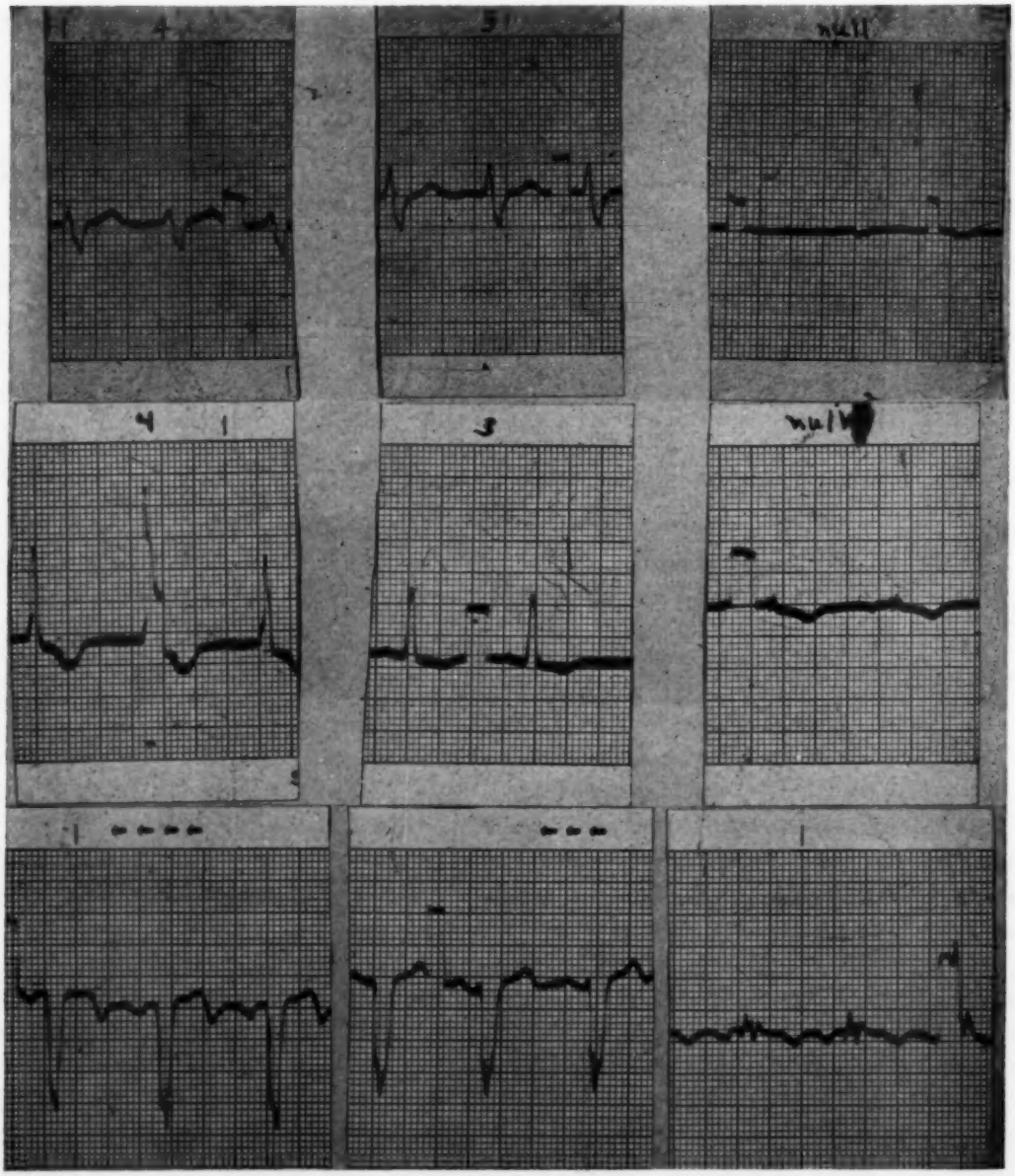

Fig. 2.—Mirror patterns and cancellations of "local" precordial patterns: *A*, Right bundle branch block; *B*, anterior myocardial infarction; *C*, left bundle branch block. In each instance, "4" represents local precordial complex*; "3" represents remote search mirror pattern, and *null* the cancellation obtained. (*Null* should also appear above the lower right portion of the illustration.)

*Complex on the precordium is deliberately inverted to compare pattern shapes.

the pattern most closely resembled that of Q versus 4. The terminal P was then adjusted on the resistor between 4 and 3 so that the recorded potential difference between P and Q was minimal. The sensitivity of the recorder was increased as necessary (up to tenfold), so that the voltage P-Q (which is the noncancelling residual of the signals Q versus 4 and 3 versus Q) could be measured. Using the location of electrode 3 and the setting of terminal P as search variables, further attempts were made to reduce the residual voltage unless it already was very small.

A cancellation coefficient was calculated for each experiment. This coefficient, defined by Schmitt, is a quantitative measure of the magnitude of the residual (noncancelling) portion of the signals, divided by a weighted average of the magnitude of the signals.

$$\text{Cancellation coefficient in per cent} = \frac{\text{residual voltage} \times 100}{(4 \text{ versus } Q)\, t + (Q \text{ versus } 3)(1-t)}$$

where t represents the fractional distance of P along the resistor from 3 toward 4.

RESULTS

In ten normal subjects, the coefficient never exceeded 15 per cent. As shown in Table I, the average coefficient was 9 per cent with a standard deviation of 3.8 per cent. In fifty-two patients with various cardiac disorders, the maximum coefficient was 19 per cent. The average coefficient varied from 8 to 12 per cent depending upon the kind of cardiac abnormality. The poorest coefficients were

TABLE I. CANCELLATION COEFFICIENTS

TYPE OF PATIENT	COEFFICIENTS REPORTED BY SCHMITT AND SIMONSON			COEFFICIENTS REPORTED IN PRESENT STUDY		
	NUMBER CASES	AVERAGE COEFFICIENT	STANDARD DEVIATION	NUMBER CASES	AVERAGE COEFFICIENT	STANDARD DEVIATION
Normal	17	11	3.7	10	9	3.8
Infarction with QRS abnormality	8	12	6.6	9	9	3.2
Emphysema	9	14	5.4			
Bundle branch block	8	21	4.5	11	12	4.7
Right ventricular hypertrophy due to congenital heart or advanced lung disease				7	12	4.8
Left ventricular hypertrophy due to hypertension or isolated aortic valve disease				11	8	2.7
Right and left ventricular hypertrophy due to rheumatic heart disease				9	11	3.6
"Ventricular strain"	9	15	4.1			
Nonspecific abnormal ECG's				5	8	3.4
Total	51			62		

observed in bundle branch block and right ventricular hypertrophy associated with congenital heart disease or far advanced pulmonary pathology. In these conditions, the average coefficient was 12 per cent, with standard deviation of 4.7 for bundle branch block, and 4.8 for right ventricular hypertrophy. Examples of mirror images and cancellations of the QRS patterns of anterior wall infarction, right bundle branch block, and left bundle branch block are shown in Fig. 2.

It is entirely probable that smaller coefficients could have been obtained in many cases. Ordinarily, each experiment was terminated when a coefficient of 10 per cent was obtained. However, prolonged efforts to reduce cancellations higher than 15 per cent were made by readjustment of the position of terminal P and of the placement of electrode 3.

DISCUSSION

A coefficient of 15 per cent indicates that 85 per cent of the two cancelling signals are identical in shape and phase (not in amplitude). Even the residual 15 per cent cannot be attributed entirely to local nondipolar influences, since many other factors contribute to it, including: technical imperfection in electrode and potentiometer placement, instrument noise, noncardiac electrical noise introduced by skeletal muscle, and movement of dipole location during generation of the QRS complex. Because the quanitative measure of cancellation is a sound criterion of the equivalent dipolar behavior of the heart, as can be shown on experimental and theoretical grounds, local current sources in heart muscle must contribute very little to patterns recorded at any specific site on the precordium. This does not imply that abnormal patterns may not appear in anatomic proximity to the site of the myocardial disorder. Dipole components of the heart may be preferentially altered in a direction related to the position of abnormal heart muscle, and proximate V-lead positions are highly sensitive to alteration in dipole components. However, it is important to note that in the same patient, some position remote from the injured area must similarly reflect these abnormal dipole components, and this latter position may be in an area not ordinarily explored in routine electrocardiography.

Although the subject material was similar in these studies, as in those of Schmitt and his assoicates, the results were not entirely comparable. Both studies revealed examples of excellent cancellation for every category of heart disease or electrocardiographic abnormality, but the spread in cancellation coefficients in various categories was much less marked in our study than in Schmitt's. None of our normal subjects had coefficients greater than 15 per cent, and none of our patients had coefficients greater than 20 per cent; however, Schmitt and Simonson found 30 to 40 per cent of patients and 10 per cent of normal subjects to have coefficients greater than 20 per cent.

In Schmitt's study, the poorest cancellation occurred in patients with bundle branch block, averaging 21 per cent with a standard deviation of 4.5 per cent. We also recorded our poorest cancellations in cases of bundle branch block where the average coefficient was 12 per cent with standard deviation of 4.7 per cent, but the difference between normal cases and cases of bundle branch block is statistically much less significant in our study than in Schmitt's.

Finally, Schmitt and his associates found significantly poorer cancellations in "ventricular strain" patients. Our results tended to confirm this finding in patients with right ventricular hypertrophy due to congenital heart disease and far advanced lung disease, but showed cancellation coefficients comparable to normal for left ventricular hypertrophy, and mixed hypertrophy associated with rheumatic heart disease.

Discrepancies in results of the two studies perhaps may be explained by two factors: (1) We spent a great deal of time searching for improved cancellations in cases where the coefficients were poor. (2) We had an additional degree of freedom in our search procedure as compared with Schmitt's, in that we were able to vary the reference terminal in any case. In no case, however, were the electrodes comprising the reference terminal permitted to come in close proximity to the precordial electrode on the site of the "local" pattern.

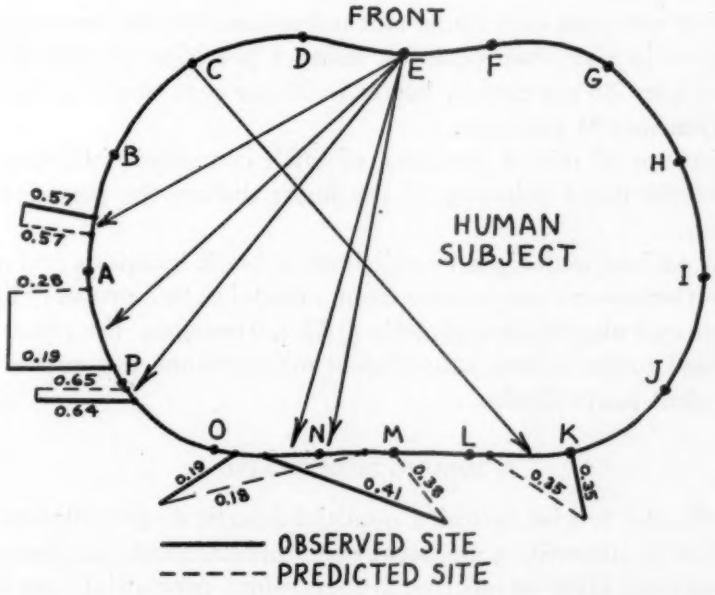

Fig. 3.—Predicted and observed sites of mirror patterns of "local" precordial right bundle branch block QRS complex of chest position *E* are shown. Mirror patterns are found at different locations depending upon the reference terminal used. Predicted and observed amplitude ratio of mirror to local precordial pattern is given for each mirror found. All mirror patterns occur in the same transverse plane, which is at the level of the electric heart center.[6] The location of the mirror pattern of chest position *C* is also shown.

As Frank demonstrated in a single normal subject, locations of mirror patterns and their relative amplitude is not a random phenomenon, but is predictable for a variety of different reference terminals from a study of the surface potentials produced on a human-shaped torso model with a properly located internal dipole. Correlation of cancellation data obtained in patients and model depends upon proper location of the dipole in the model. This has been used as a basis for location of the heart dipole anatomically in forty of the patients of this study, and is the subject of a recent report.[7]

In a case of right bundle branch block, the dipole was satisfactorily located equivalent to position 04 of the Frank torso model.[6] It was then possible to predict for any reference terminal used, the amplitude and location of mirror patterns of the "local" right bundle branch block QRS from the medial precordium. Predicted and observed mirror image locations and amplitudes for this case are indicated in Fig. 3. Excellent correlation between observed and predicted patterns indicates the validity of the assumption of homogeneity of body tissues and the importance of dipole location effects on body surface potentials.

Results of this entire study show that the concept of localized currents producing localized electrocardiographic QRS patterns is unsound. Rather, they indicate that equivalent dipole representation of electric activity of ventricular depolarization is accurate in patients to a degree of 80 per cent or better.

SUMMARY

1. Mirror patterns were found on the body surface for normal and abnormal QRS complexes in sixty-two patients, using a precision cancellation technique. Cancellations were 85 per cent or better in 90 per cent of the patients; the poorest cancellation was 81 per cent.

2. Existence of mirror patterns of QRS complexes indicates the dipolar nature of the electrical behavior of the heart during the period of ventricular depolarization.

3. In a patient with right bundle branch block locations and amplitudes of the mirror patterns were predictable from a model with a properly located dipole.

4. Localized electrocardiographic QRS patterns on the chest wall are not due to localized currents from subadjacent myocardium, but rather to alteration of the equivalent heart dipole.

SUMMARIO IN INTERLINGUA

Per medio del precise technica quadrielectrodic de cancellation disveloppate per Frank, nos ha succedite a monstrar experimentalmente que imagines specular del configurationes QRS in electrocardiogrammas precordial, con cancellationes de 80 pro cento o plus, esseva presente in registrationes ab cata un de 10 individuos normal e 52 patientes cardiac con varie typic configurationes electrocardiographic. Le discoperta del configurationes specular non presupponeva le uso de un particular terminal de referentia. Super le base de datos derivate ab experimentos con le modello del torso human, il esseva possibile—usante varie terminales de referentia—predicer le location e le magnitude de imagines specular del typic precordial complexo QRS in un patiente con bloco de branca dextere. Nos conclude que precordial complexos QRS non es debite primarimente a localisate currentes ab areas subadjacente myocardial sed plus tosto a un alteration in le equivalente dipolo cardiac. Es discutite certe similitudes e differentias de methodologia e del resultatos inter le presente studio e le studios de configurationes specular executate per Schmitt e su associatos.

We are indebted to Miss Cynthia Hamilton for technical assistance, and to Drs. Ernest Frank and Calvin F. Kay for advice and encouragement.

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THE MECHANISM OF COUGH SYNCOPE

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ALTHOUGH described in 1876 by Charcot,[1] the syndrome of cough syncope has until recently been considered a rare form of fainting. However, the excellent reports by Baker,[2] Sharpey-Schafer,[3] and Kerr and Derbes,[4] indicate that the condition may not be uncommon. Despite increasing recognition of the syndrome, the mechanism producing the syncope remains elusive.[4]

Earlier investigators have suggested that this form of syncope is an epileptic equivalent[5-7] or the result of a laryngeal reflex.[6,8] These theories, however, have generally been abandoned in favor of a circulatory mechanism producing cerebral anoxia.[9] It has been suggested that the cerebral anoxia might be the result of marked reflex peripheral vasodilation[3] or a decreased cardiac output secondary to a reduced inflow or marked pulmonary vasoconstriction.[10]

These theories, though attractive, fail to explain completely certain unique features of this form of syncope. For example, syncope may develop with remarkable rapidity (3 to 5 seconds) after the onset of cough. With the cessation of cough, consciousness is rapidly recovered without vasomotor or other sequelae. The syndrome is rarely observed in women and syncope may occur in the supine or standing subject.

The present report, based on observations made on normal individuals and patients with cough syncope, suggests a more acceptable mechanism for this type of fainting.

MATERIALS AND METHODS

Twenty patients who had experienced cough syncope were questioned in detail regarding these episodes. Studies were undertaken on thirteen of these patients to determine the effect on the cardiorespiratory system of single and paroxysmal coughs. The intrathoracic pressure was measured by an air-filled

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This study was carried out during Dr. McIntosh's tenure as an American Heart Association Fellow and Dr. Estes' tenure as the Alfred Stengel Fellow of the American College of Physicians.

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esophageal balloon.[11] The systemic arterial pressure and the cerebrospinal fluid pressure were measured through indwelling needles. These pressures were recorded simultaneously by a suitable Statham strain gauge or a Sanborn electromanometer on a Sanborn four-channel direct-writing oscillograph. In some studies the "net" pressure,[12] the arterial pressure minus the intrathoracic or spinal fluid pressure (see discussion), was recorded by a Statham differential strain gauge. For comparison, similar studies, completely or in part, were made on a heterogenous group of 100 patients with no history of cough syncope.

RESULTS

The clinical features of the syndrome of cough syncope have been adequately described.[2,4] The twenty subjects in this study were comparable to those previously reported. Syncope could be produced at will in only one individual, in whom eight episodes were observed. It is likely that syncope could not have been produced in more subjects because the paroxysms of cough were voluntary rather than spontaneous, the latter being more forceful. Then, too, these studies were carried out with the patient in the supine position. Although this form of syncope occurs in the supine subject, it more readily occurs when the subject is in the upright position.

The observed episodes of syncope followed a definite pattern. When syncope occurred it followed a paroxysm of cough of an explosive and vigorous character. The paroxysm was not usually interrupted by inspiration. It appeared to be produced by powerful muscular contraction of not only the thorax, but also the abdomen. The patient stated that this type of cough differed from his usual nonproductive cough; once begun it usually could not be controlled.

Two to three seconds after the onset of such a paroxysm of cough, the patient's eyes became fixed straight ahead. In retrospect the subject stated that about this time his vision became less acute, and there was a loss of peripheral vision and color sense so that everything appeared gray. At this time the patient could hear commands but was unable to respond. If the cough ceased, no additional symptoms developed and he promptly returned to his normal mental state. However, if the cough continued, within a second or two the eyes turned upward, and the patient lost consciousness and became flaccid. Simultaneously with the loss of consciousness the cough ceased. Within two seconds after the loss of consciousness, clonic twitchings were occasionally observed in the orbicularis oris and muscles of the right hand. Consciousness was regained within ten seconds, and for five to ten seconds the patient was confused, but then promptly became completely oriented. When again mentally clear, the subject had amnesia for the episode and was not certain that he had lost consciousness. There were no vasomotor manifestations, incontinence, or other sequelae associated with the syncope. The entire episode, including the postsyncopal confusional state, lasted only about thirty seconds. Three episodes of syncope occurred while in the sitting position. Consciousness was regained promptly without placing the patient in the supine position. The remaining episodes of syncope occurred while the subject was supine.

Hemodynamic Alterations.—The hemodynamic alterations produced by single coughs or paroxysms of cough were qualitatively the same in patients with cough syncope and normal subjects. A single cough caused a rise in the arterial pressure contour. This rise was perceptible with coughs of very minimal intensity (6 to 8 mm. Hg); it was progressively larger with coughs of larger amplitude. The rise in the arterial pressure was usually smaller in magnitude than the rise in intrathoracic pressure accompanying the cough (Fig. 1).

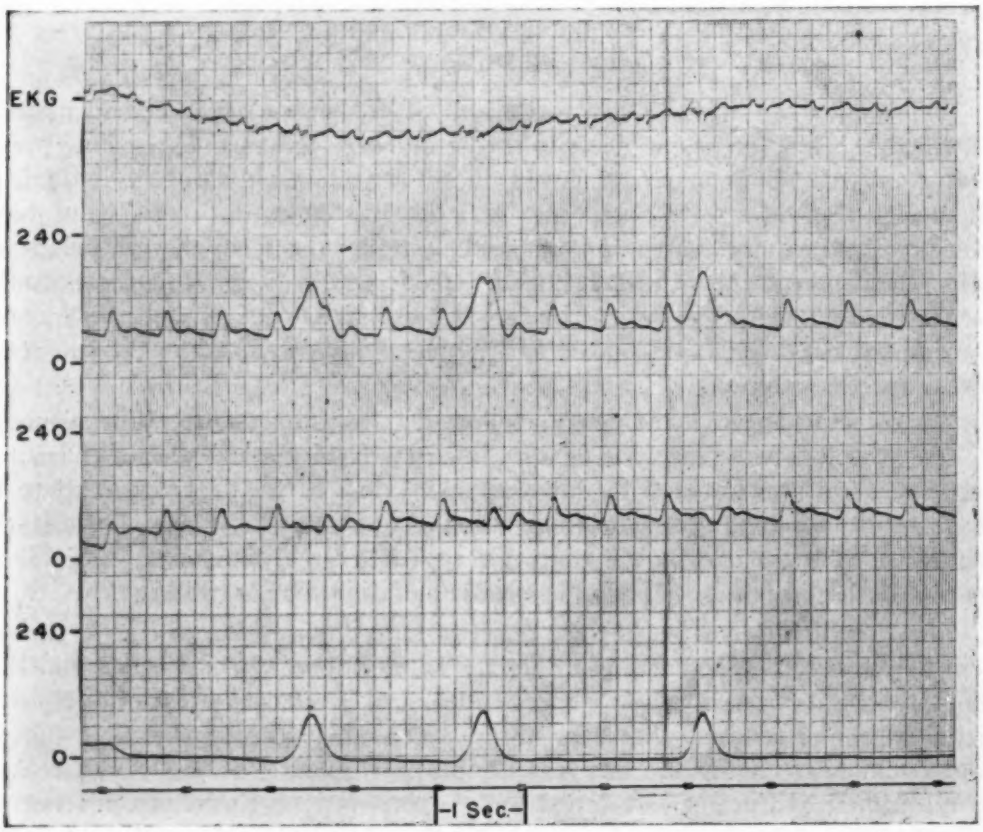

Fig. 1.—The changes of intrathoracic pressure produced by a single cough are recorded in the lower tracing through an esophageal balloon. Such elevations of intrathoracic pressure produce changes in the brachial arterial pressure. However, the increase of arterial pressure is not as great as the increase of intrathoracic pressure. The differential, or "net" pressure (see text), therefore, is lower during the cough than the arterial pressure would have been in the absence of the cough. *A*, Brachial arterial pressure; *B*, Differential (brachial artery-esophageal) pressure; *C*, Intrathoracic (esophageal) pressure.

A paroxysm of cough, whether continuous (Fig. 2) or intermittent (Fig. 3), produced a more obvious alteration of the arterial pressure curve; though, again, the magnitude of the rise in arterial pressure was usually less than the rise in intrathoracic pressure accompanying the paroxysm. It was noted, however, that intermittent coughs of the same magnitude often caused smaller and smaller rises in arterial pressure (Fig. 3). The differential (brachial arterial minus intrathoracic) pressure was observed to decrease with each cough or paroxysm of cough (Fig. 3).

Upon cessation of a continuous or intermittent paroxysm of cough, the arterial pressure was considerably below the precough level. It generally rose gradually and within five to fifteen seconds equalled or slightly exceeded the precough level. This period of relative hypotension was not associated with a consistent change in cardiac rate.

Simultaneous recording of arterial, intrathoracic, and cerebrospinal pressure was carried out in five normal patients and six patients with cough syncope.

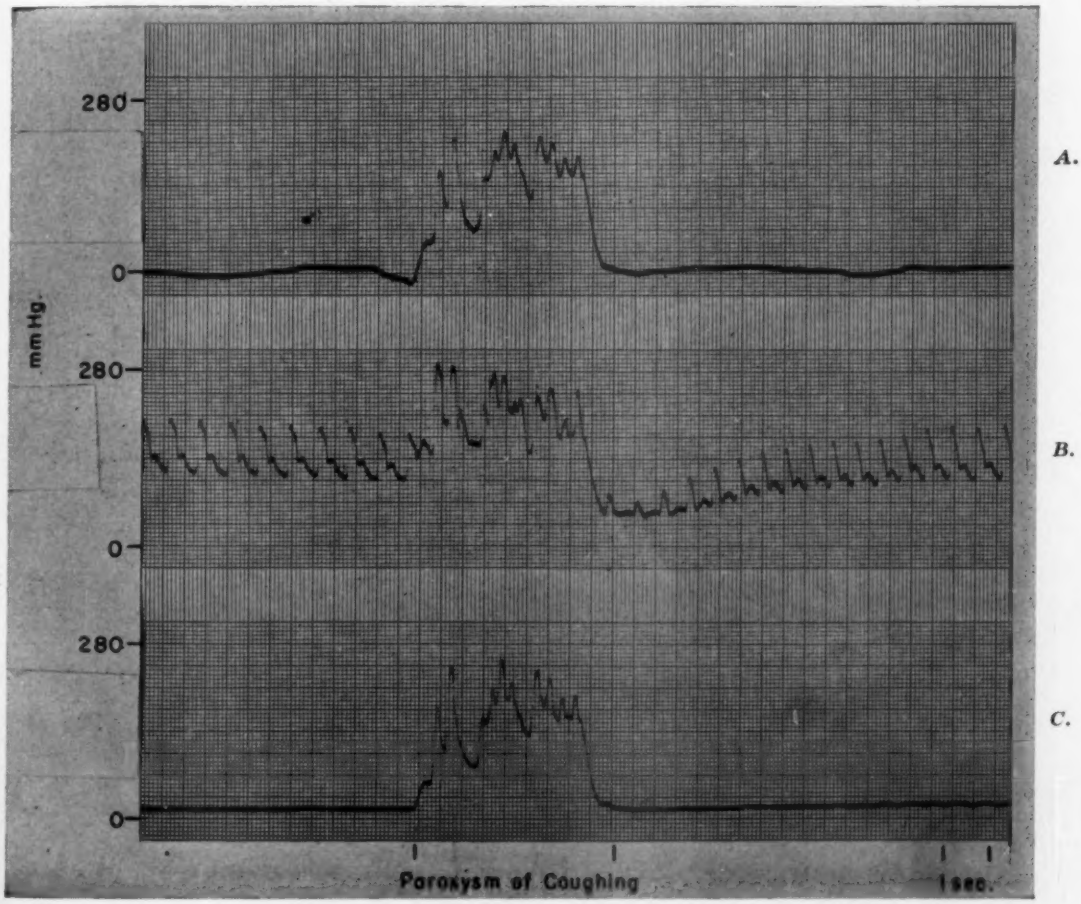

Fig. 2.—This patient had experienced numerous episodes of cough syncope. Syncope was usually associated with a continuous paroxysm of cough such as recorded in this tracing; however, it did not occur on this occasion. The cerebrospinal fluid pressure rose to 250 mm. Hg and reflects with remarkable fidelity changes of intrathoracic pressure. Observe the low arterial pressure present at the cessation of cough. *A*, Esophageal (intrathoracic) pressure; *B*, Bronchial arterial pressure; *C*, Cerebrospinal fluid pressure.

With cough, the cerebrospinal pressure rose to essentially the same level as did the intrathoracic pressure. This rise in spinal fluid pressure occurred without significant delay (Figs. 2 and 4). The arterial pressure elevation due to cough was, therefore, not as great as the rise of intrathoracic or cerebrospinal fluid pressure.

As noted previously, the response of normal subjects and patients with a history of cough syncope was qualitatively the same. The chief difference in the two groups is that patients with cough syncope can cough more forcefully and continue the cough longer than normal subjects. It was not uncommon to see coughs in the syncope group causing increases of intrathoracic and cerebrospinal fluid pressure approaching 300 mm. Hg. These observations are in agreement with those of Sharpey-Schafer.[3]

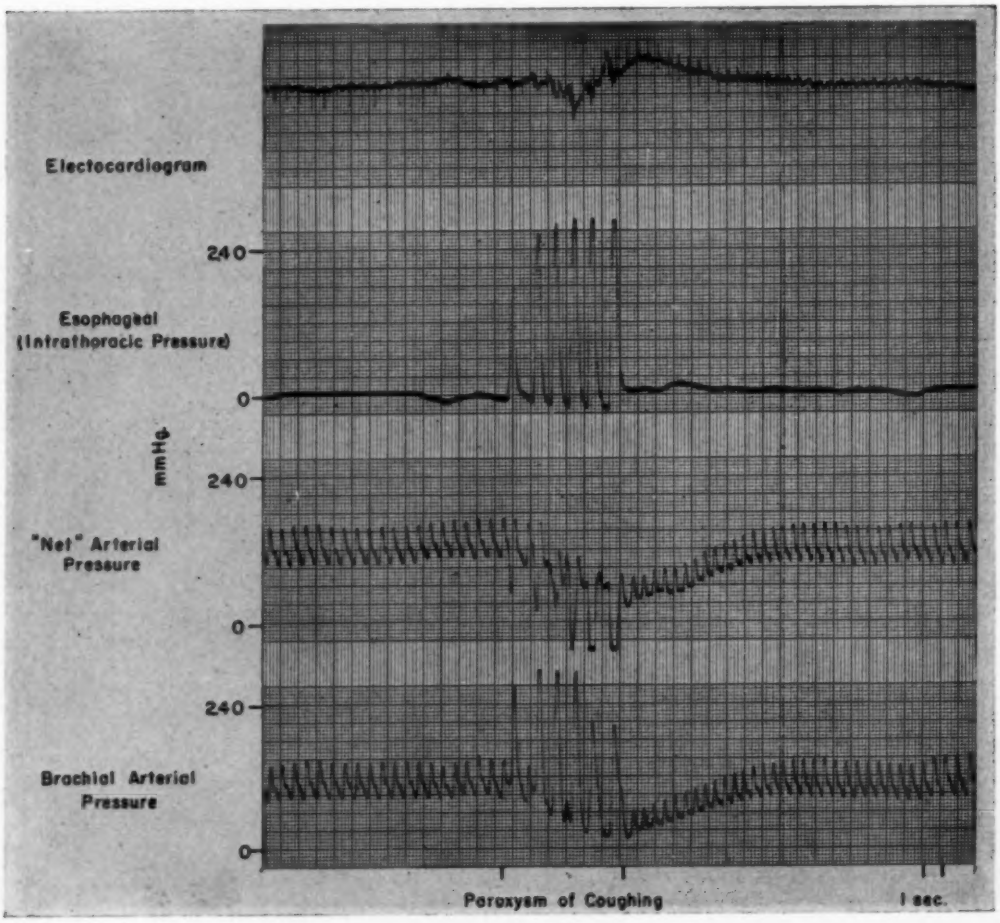

Fig. 3.—This tracing records a series of intermittent coughs in the same patient studied in Fig. 2. Successive coughs produce slightly greater rises of intrathoracic pressure, but are associated with progressively smaller elevations of the brachial arterial pressure. The "net" or differential pressure is, therefore, intermittently below zero. The patient did not faint on this occasion.

DISCUSSION

Sharpey-Schafer[3] and Kerr and Derbes[4] have suggested that the syndrome of cough syncope is not uncommon. Observations in this laboratory are in complete agreement with these workers. The first eighteen of the twenty patients who form the basis of this report were admitted to the Medical Service

of the Durham Veterans Administration Hospital during a six-month period from March, 1954, to September, 1954.

Only three of the twenty patients were admitted to the hospital with a primary complaint of syncope. Although most of these patients had a chronic cough, they did not spontaneously relate the history of fainting following cough. This information was obtained only by direct questioning. Thus, the incidence of cough syncope is dependent on the extent to which one probes for the symptoms of the syndrome.

The clinical features of the syndrome have been adequately described[2,4]; however, certain observations are worthy of specific emphasis. As previously noted, syncope may occur rapidly (3 to 5 seconds) after the onset of a paroxysm of cough and may be observed in the supine subject. It has been reported to

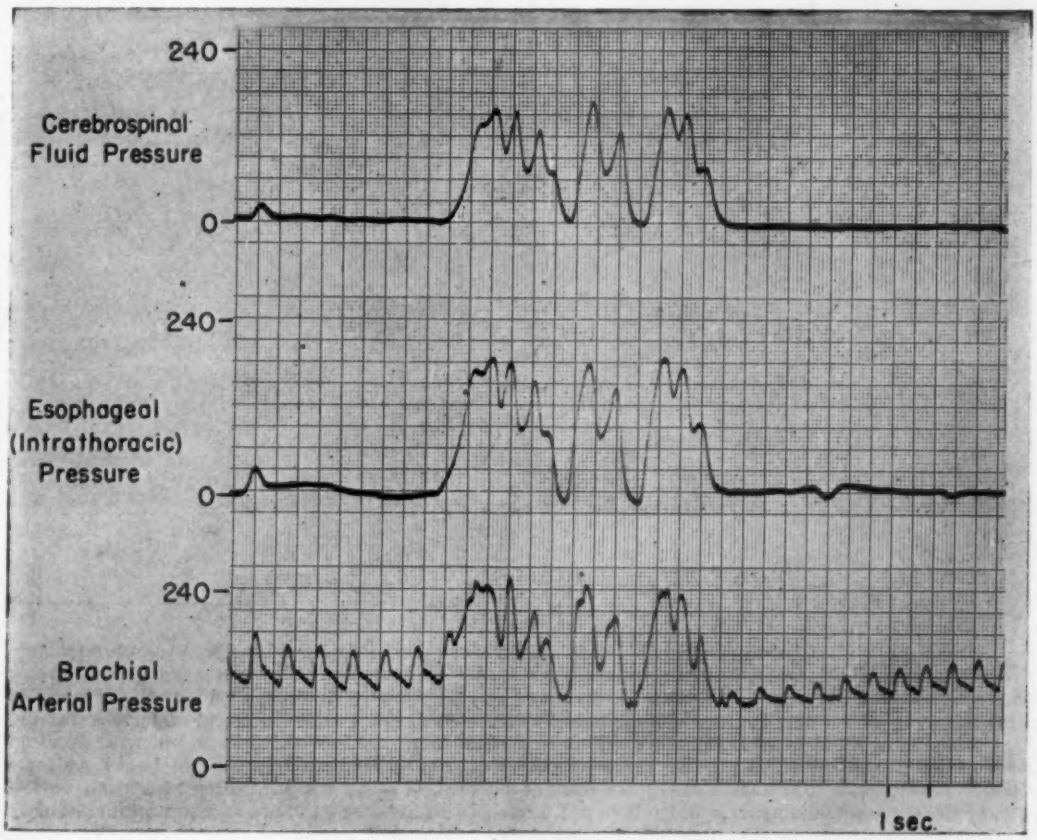

Fig. 4.—This patient had a history of cough syncope. Note the remarkable similarity between the cerebrospinal fluid and intrathoracic pressures.

have followed a single cough (usual duration 0.2 to 0.3 second)[2,4]; however, some observers,[3] including the writers, consider such reports with skepticism. The condition is rare among women. Only three of two hundred and ninety reported patients were women.[4] Consciousness may be regained following syncope in the sitting position without placing the subject in the supine position. There are no vasomotor or other sequelae.

It has been observed in this and other laboratories[13] that changes of intrathoracic pressure are transmitted with great fidelity to the cerebrospinal fluid compartment (Figs. 2 and 4). Myelograms have been performed in upright patients while standing quietly and while performing the Valsalva maneuver.[14,15] When the intra-abdominal pressure is increased, the subarachnoid space narrows (Fig. 5) and the nerve roots are displaced medially.[14] Therefore, the rise in intrathoracic pressure produces an enlargement of the epidural space and the spinal fluid pressure rises. This increase of the epidural mass is thought to be

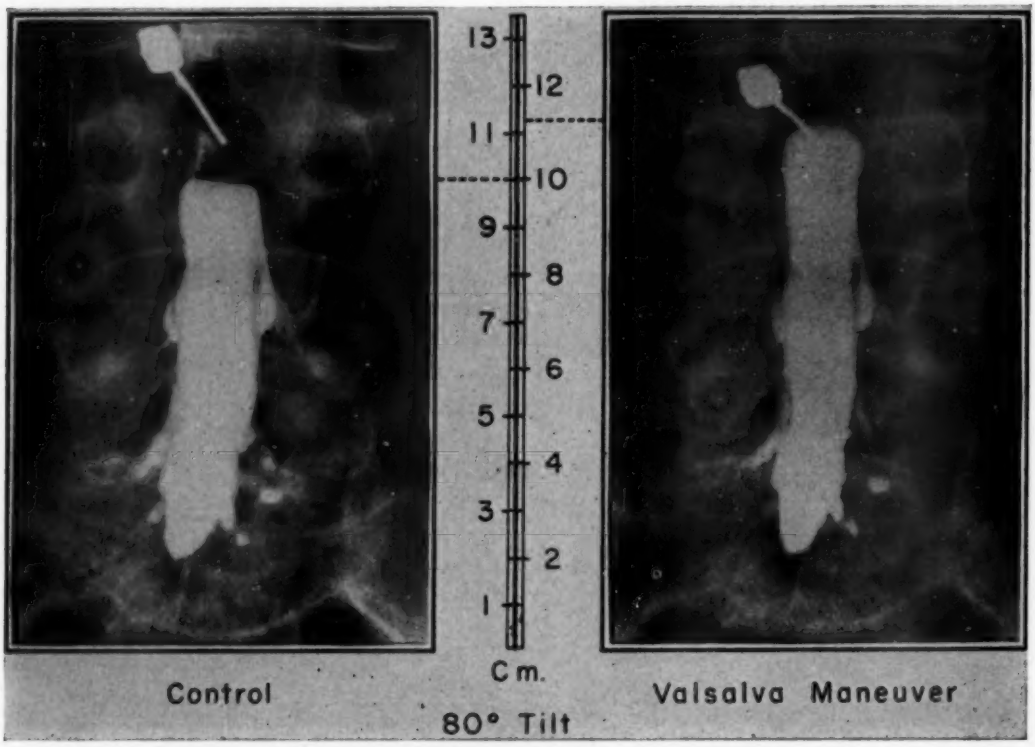

Fig. 5.—The myelogram on the left was obtained while the patient was motionless at an 80-degree head up tilt; that on the right while performing a Valsalva maneuver. The increase in intrathoracic or intra-abdominal pressure was not measured during this maneuver. The height of the column of Urokon increased 1.3 cm. due to engorgement of the vertebral veins in the epidural space. Assuming that the subarachnoid space is a perfect cylinder and that increased intrathoracic and intra-abdominal pressure is transmitted equally to the epidural space along the entire length of the spinal cord, a simple calculation indicates that during the above maneuver 23 ml. of blood was "squeezed" from the vessels within the subarachnoid space. Since it is not known to what extent the above assumptions actually apply, this calculation may involve considerable error.

the result of engorgement of the epidural veins due to the shunting of blood from the abdomen and thorax. This shunting of blood from the abdominal to the vertebral veins during increased intra-abdominal pressure was demonstrated radiographically by Batson[16] in the monkey. The movement of loose fatty and areolar tissue and the spinal nerve roots into the spinal canal may also aid in compressing the subarachnoid space.[13]

The validity of using the esophageal pressure as a measure of intrathoracic pressure has recently been questioned.[17] The marked similarity of changes of

the esophageal and cerebrospinal fluid pressures suggests that the esophageal pressure reflects the intrathoracic pressure quite accurately.

A cough, therefore, causes an essentially equal rise in intrathoracic, intra-abdominal, and intracranial pressure (Figs. 2 and 4). There may, however, be minor differences in the increases of pressure above and below the diaphragm due to the tone of the abdominal muscles and the diaphragm.[15,18] It would seem that the rise in cerebrospinal fluid pressure represents essentially the mean of the pressure rises in the two cavities of the trunk.

Sudden increases of intrathoracic pressure, as with cough, result in a sudden rise of the peripheral arterial pressure (Figs. 1 and 2). This same rise also occurs in the thoracic and abdominal aortic pressure.[15] In contradistinction to the aortic pressure, the rise of the peripheral arterial pressure is associated with little or no increase in extravascular pressure.

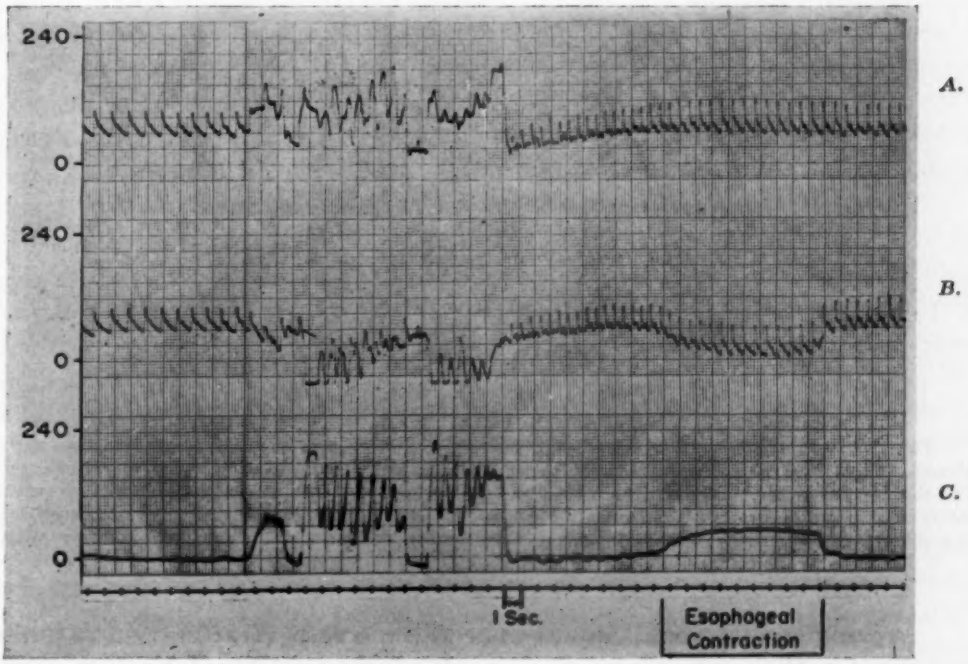

Fig. 6.—This patient had numerous episodes of syncope following cough. Observe that the differential ("net") pressure is almost zero or below for several seconds. *A*, Brachial arterial pressure; *B*, Differential (brachial arterial-esophageal) pressure; *C*, Intrathoracic (esophageal) pressure.

The effective distending pressure, or that pressure which prevents the collapse of a vessel, is equal to the intraluminal pressure (recorded by an indwelling needle) minus the extravascular pressure.[19] Hamilton[12] has referred to this pressure as the differential or "net" pressure.

In the absence of increased intrathoracic, intra-abdominal, or intracranial pressure, the extravascular pressure throughout the body in the supine subject is essentially equal. Changes in intrathoracic, intra-abdominal, or intracranial pressure do not alter the extravascular pressure outside these cavities.

Therefore, during cough the "net" peripheral arterial pressure is the same as the observed pressure. However, the "net" pressure of the arteries within the thorax and abdomen is equal to the peripheral arterial pressure minus the increase in intrathoracic or intra-abdominal pressure (Figs. 3 and 6). It follows that the "net" intracranial arterial pressure is equal to the peripheral arterial pressure minus the increase of cerebrospinal fluid pressure. In this study the "net" pressure was recorded by a Statham differential strain gauge and represents the peripheral arterial pressure minus the rise of intrathoracic or cerebrospinal fluid pressure.

The observed rise in arterial pressure due to cough is usually significantly less than the rise of the intracavitary pressure. Thus, during a cough the "net" pressure in the vessels of the thorax, abdomen, and cranium are less than during the precough period (Figs. 3 and 6).

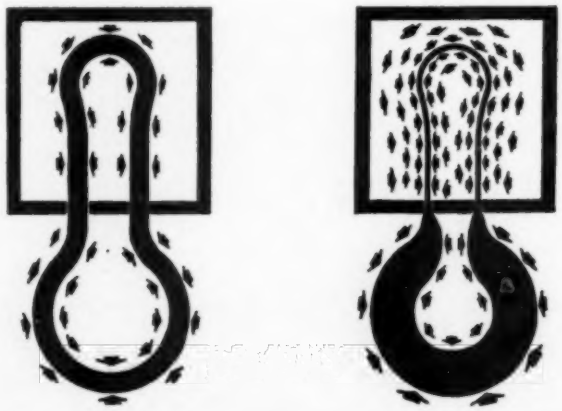

Fig. 7.—In this sketch, the square box represents the cavities of the body, i.e., the thorax, the abdomen, and the cranium. The vascular system is represented as being only partially intracavitary. The sketch on the left represents the condition existing before cough, that on the right represents the condition existing during cough. During cough the intracavitary pressure is markedly increased, leading to a collapse of the intracavitary vessels and a "squeezing" of blood into the extracavitary vessels.

Accordingly, it would appear that the increase of intracavitary pressure associated with cough might mechanically "squeeze" blood from the vessels, both arteries, and veins in such cavities to regions not subjected to increased extravascular pressure (Fig. 7). These regions would be the skin and muscles of the trunk and head, the neck, and the extremities. Plethysmographic studies[15] of an extremity were carried out and demonstrated an increase in the volume of the extremity during cough.

The principal obstruction to redistribution of the blood is the distensibility and the capacity of the vessels outside the area of increased vascular pressure. This problem has been investigated in this laboratory[15] by means of glass and rubber models. It was demonstrated that the degree of transmission of increases of the pressure in the compression chamber (simulating the thorax) to the simulated vascular system was dependent on the distensibility of that part of the vascular system outside the compression chamber. If the system

was absolutely rigid, the pressure changes in the simulated thorax and extrathoracic vascular system were identical and the "net" pressure was unchanged. On the other hand, if the tubes outside the compression chamber were highly distensible, then fluid was displaced into them by an increase of pressure in the compression chamber. The "net" pressure within the simulated thoracic vessels was thus reduced and these tubes could be seen to partially collapse.

As previously pointed out, the circulatory response to cough was qualitatively the same in normal subjects and those with cough syncope. The only demonstrable difference between the two groups was that patients with cough syncope were able to cough more forcefully than normal patients; whether this be a manifestation of body build, compliance of the pulmonary system, or other unknown factors is at present uncertain. However, it was not uncommon to observe in subjects with a history of cough syncope, sudden increases of intrathoracic and spinal fluid pressures approaching 300 mm. Hg. This remarkable increase in intracavitary pressure resulted in the "net" arterial pressures in the thorax, abdomen, and cranial vault approaching or equalling zero (Figs. 2 and 6). If such a paroxysm of cough was prolonged, the "net" pressure in the thorax, abdomen, and cranium would become and remain essentially zero for several seconds. The intracavitary vessels apparently would be collapsed and cerebral anoxia and syncope would occur. Women do not experience cough syncope because they cannot cough forcefully enough[3] to produce such changes.

In many subjects the "net" intracavitary arterial pressure during a paroxysm of cough did not reach the lowest level for several seconds (Fig. 3). This delay is possibly due to reduced inflow into the right heart or to a vasodepressor reflex from areas such as the carotid sinus, resulting in vasodilatation. If vasodilatation occurred in the periphery, blood could more easily be "squeezed" from the high pressure cavities to the periphery. It would appear that syncope due to cough results from the mechanical effect of a sudden increase of extravascular pressure which may well "squeeze" blood from the cranial vault, thus rendering the brain essentially "bloodless" (Fig. 7).

The rapidity of onset of syncope even in the supine position demands special comment. An asystole of four to eight seconds may result in unconsciousness in the erect subject, whereas an asystole of at least twelve to fifteen seconds is necessary to produce unconsciousness in the supine subject.[20] In such a situation, despite asystole, there is still a flow of blood through the capillary bed due to the arteriovenous pressure gradient present at the time of the last systolic contraction. Also the cerebral vessels, despite a negligible flow, are always filled with blood from which oxygen may be extracted. Marked vasodilatation or a markedly decreased cardiac output, for the same reason, would likewise not produce syncope as rapidly as it occurs following cough. However, it appears that a sudden increase of intracavitary pressure actively "squeezes" and shunts blood from the cerebral vessels and suddenly renders them essentially "bloodless."

The rapidity of onset of syncope is of further interest in view of the report of Rossen and associates,[1] describing the production of unconsciousness by sudden complete occlusion (by neck tourniquet inflated to 600 mm. Hg) of arterial in-

flow to the head. Rossen found that the average time required for unconsciousness was 6.5 seconds in a group of 137 individuals. The variability from patient to patient was rather large, the range being from five to eleven seconds in the sitting subject. This variability was thought to be related to individual variations in the time with which the brain exhausted the oxygen supply in the blood trapped in the cerebral capillary bed by the occluding cuff. Syncope due to cough might be expected to occur more rapidly than syncope due to neck compression, for it is unlikely that significant blood is trapped in the cerebral capillary bed in the former condition.

Rossen[21] calculated that, with sudden occlusion of arterial inflow to the head, approximately 95 c.c. of blood was trapped in the brain. Clinical observations of subjects during a marked paroxysm of cough would suggest that this relatively small quantity of blood could be readily "squeezed" into the muscles and skin of the head, face, and neck and leave the brain relatively "bloodless." It should be noted that blood could be "squeezed" from the cranium not only by way of the carotid arteries and jugular veins, but also by numerous anastomotic channels of the diploic, the emissary, and the ophthalmic veins. There exists between these extradural veins a rich anastomoses with intradural veins. This rich venous plexus, including the vertebral veins, serves as a reservoir to help maintain an equilibrium between changes of pressure of the cerebrospinal fluid and the cerebrovascular system. A rise of cerebrospinal fluid pressure would result in an expulsion of blood from the intracranial vessels to that part of the reservoir not subjected to a similar pressure rise.

Despite a recent report by O'Doherty[7] of five patients with a history of cough, an abnormal electrocephalogram and/or convulsions, vertigo, and syncope, the observations of this study agree with those of most contemporary investigators[2-4,10] there is little evidence that cough syncope is a form of epilepsy. Undoubtedly, epileptics may cough before, during, or after a seizure. We have studied an individual, not included in this report, who had what appeared to be both psychomotor seizures and cough syncope. It would be expected that a subject with an abnormal electroencephalogram might well be more susceptible to the anoxia produced by a cough paroxysm and, thus, faint more easily. However, it would not appear that an abnormal cerebral cortex is necessary for cough syncope to occur. Electroencephalograms were recorded from five patients in this series and one showed minimal abnormalities. Because of the marked muscular activity associated with a cough paroxysm, it has been impossible to record the cortical activity during or immediately after a cough paroxysm.

The symptomatology of cough syncope is not unlike that associated with mild cerebral concussion. Denny-Brown[22] defined this latter condition as an immediate, transitory, and rapidly reversible nervous reaction following brief but violent physical stress. Upon regaining consciousness the subject has both retrograde and postgrade amnesia for the episode. Apparently the signs observed following concussion result from a reaction to physical condensation of the nervous system due to a stress of only a fraction of a second duration.

Amnesia for the syncopal episode associated with cough and the rapid recovery of consciousness with only minimal sequelae is well documented. One might wonder if the sudden rise of spinal fluid pressure resulting from increases

of intrathoracic pressure due to cough could cause a physical condensation of the nervous system following a single cough. However, such an occurrence is highly doubtful. It would seem rather that cough syncope occurs only after the cerebrospinal fluid pressure has been elevated for several seconds. The cerebral arteries and veins are freely collapsible and, especially the veins are richly anastomosed to the extracranial vessels. The collapse of these vessels would apparently protect the brain from a sudden impact of the major increment of the increase of cerebrospinal fluid pressure due to cough. Therefore, it appears unlikely that the mechanism of cough syncope is similar to that producing concussion.

SUMMARY AND CONCLUSIONS

1. The effect of cough on the cardiorespiratory system in thirteen patients with cough syncope and a group of 100 normal patients is reported.

2. The response to cough in these two groups of patients differed only in magnitude; i.e., patients with cough syncope were able to cough more forcefully and for a longer duration than normal patients.

3. These studies suggest that syncope due to cough is the result of the transmission of markedly elevated intrathoracic and intra-abdominal pressure to the cerebrospinal fluid compartment causing an essentially equal rise of the latter pressure. This increased cerebrospinal fluid pressure, by increasing the extravascular pressure around the cranial arteries and veins, causes blood to be "squeezed" from the cranium. Thus, the brain becomes rapidly "bloodless," anoxia develops, and syncope may occur.

4. As in most physiologic events the occurrence of cough syncope apparently depends on many variables. Of primary importance is the magnitude and duration of the cough paroxysm, which possibly depends on the body build and the compliance of the pulmonary system. The facility with which blood may be "squeezed" from the cranial vessels is also of importance and apparently depends on the dynamic distensibility of the vascular system not subjected to an increased extravascular pressure, the cardiac output, the total blood volume, and other at present unknown factors. Lastly, the susceptibility of the cerebral cortex to anoxia would determine the duration of time that a "bloodless" brain must be maintained for syncope to occur.

5. The results of this study are in agreement with other reports[2-4] which suggest that cough syncope is a common form of fainting.

SUMMARIO IN INTERLINGUA

Ben que on ha asserite que syncopes tussic representa un forma non incommun de syncope, le mechanismo que produce los ha non essite clarmente elucidate. Observationes presentate in iste studio suggere que syncopes per tusse resulta ab le practicamente non reducite transmission de marcatemente augmentate pressiones intrathoracic e intra-abdominal verso le compartimento de fluido cerebrospinal. Iste augmentate pression del fluido cerebrospinal augmenta le pression extravascular circa le arterias e venas cranial con le effecto de un exprimition de sanguine ab le cranio. Assi le cerebro es rapidemente disproviste de sanguine. Il resulta anoxia, e syncope occurre.

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THE ELECTROCARDIOGRAPHIC EXERCISE TEST: CHANGES IN THE SCALAR ECG AND IN THE MEAN SPATIAL QRS AND T VECTORS IN TWO TYPES OF EXERCISE; EFFECT OF ABSOLUTE AND RELATIVE BODY WEIGHT AND COMMENT ON NORMAL STANDARDS

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ELECTROCARDIOGRAPHIC evaluation of the effect of exercise is increasingly popular and, indeed, would seem to have considerable value. In view of the large literature on the subject—Scherf and Schaffer[1] list eighty-five references in an excellent review—the lack of standardization on the exercise to be used and the absence of adequate standards of normality are notable. Standards of normality data for different ages and relative body weights are available for the conventional resting electrocardiogram[2] and for different relative body weights for the mean spatial QRS and T vectors,[3] but nothing comparable has been published for exercise tests.

In Master's two-step test[4-6] the exercise load, as number of ascents to be made, is varied according to age and absolute body weight. This implies that older and heavier persons are expected to show greater electrocardiographic deviations after a given exercise. No electrocardiographic evidence for this has been reported, but it is assumed that the same standard procedure developed for the evaluation of pulse rate and blood pressure[7,8] may also be suitable for electrocardiographic studies. Whether, in fact, the recommended gradation of exercise is proper for pulse rate and blood pressure evaluation will be discussed below.

There is clearly an effect of age on the electrocardiographic response to exercise. Mazer and Reisinger[10] noticed an age trend in the S-T segment after the two-step test and this was confirmed by Silver and Landowne[11] with the double two-step test. In comparisons of 30 young men and 100 middle-aged men walking on the treadmill, there were statistically significant differences in the postexercise heart rate, depression of the S-T segment in V_5, right shift of the T axis and decrease in ΣT.[9]

The question as to the influence of body weight is more complex. Master corrected his work load (number of ascents) for the absolute body weight, but there is reason to believe that the relative body weight should be more properly

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used for this. Increase of body weight by muscle mass or by fat (high relative body weight) is physiologically not equivalent, since fat, in contrast to muscle, is an inert load. Therefore, an analysis of the effects of absolute and relative body weight (per cent over- or underweight) is important and will be made below.

A second aspect of the present study is concerned with a comparison of two different types of work. Various types of work have been suggested by different authors for electrocardiographic exercise tests, but no evaluation of differences between different types of exercise has been reported.

The basic principle of an exercise tolerance test is the concept that valuable information will be obtained from the response to a known or fixed increase of the metabolic and circulatory load. During the steady state, there is a high correlation between work load, metabolic rate, and respiratory and circulatory changes, but in the initial phase of adaptation, i.e., for the first three to five minutes of work, the correlation is poor.[12] Therefore, a test involving aerobic work (not involving a large oxygen debt) and of sufficiently long duration to reach the steady state would seem to be preferable to work of shorter duration. Because of the absence of significant training trends,[13] walking on the treadmill appears to be an ideal type of work for an exercise tolerance test. Walking is the most common type of exercise and, consequently, symptoms of angina pectoris are usually first noticed when walking. However, treadmills are available only in a very few hospitals and laboratories and a simple standardized test which can be used without limitations of cost or space is needed as a substitute. A step test, such as introduced by Master and Oppenheimer,[7] is well suited for this purpose, although, due to the short duration (one and one-half or three minutes), the steady state is not reached. Our material, therefore, includes a comparison of the electrocardiographic response after walking on the treadmill and after a step test.

The third aspect of this study is a comparison of conventional electrocardiographic items and mean spatial vectors after exercise. The normal standard material as well as the abnormal material available so far is based on conventional ECG items, mainly the S-T segment and the T wave. While scalar leads are better for recognition of changes in the S-T segment, it is quite possible that the occurrence of significant changes in direction and magnitude of electrocardiographic vectors may have been overlooked. Comparison of different levels of severity of exercise in a small group revealed, indeed, significant differences of mean spatial QRS and T vectors[14] but no "normal" standards have been reported so far for a larger group.

METHOD

Exercise.—A. Walking on the motor-driven treadmill was standardized for a duration of ten minutes at a speed of 3 miles per hour and a grade of 5 per cent.

B. Stepping up and down a step of 12-inch height at a rate of 19 ascents per minute, regulated by a metronome, was performed for a total of forty-seven ascents, amounting to slightly over two and one-half minutes. The

metronome was set at 76 beats per minute, allowing two beats for stepping up and two beats for stepping down, using alternately the right and the left leg for stepping up to avoid muscular fatigue. Preliminary experiments were made with Master's arrangement of two steps, each 9 inches high. The necessity of the subject turning around was felt to be awkward. There is no reason why the two-step test cannot be replaced by the simpler one-step test with the same step height doubling the number of ascents. We found that the height of the steps could be increased to 12 inches without any inconvenience for normal subjects or patients, and that this allowed the duration to be shortened to about two and one-half minutes. The total distance of lift is between that of Master's single and double-step test. However, we consider the height of the steps (9 or 12 inches) of comparatively minor importance, since, by variation of the duration, equivalent work can be easily obtained. Since Master varies the number of ascents at the same duration of work, the actual variable is the rate, which is, however, not rigidly controlled in his hands. In our procedure, the rate, total number of ascents, and duration are rigidly controlled and are the same for all individuals, since the response of different categories of subjects to a standard exercise is compared. Walking on the treadmill was performed in the winter, in 1953, and the step test was studied one year later on the same subjects. There was no significant difference in the group means and standard deviations of the resting ECG (conventional items as well as spatial vectors) within that year.

Electrocardiograms.—Three standard leads and six to eight precordial leads were taken in the basal condition before exercise and in the first and third minute of recovery after exercise. Since in normal persons and in most patients the most significant changes occur in the first minute of recovery, the present discussion is limited to this time interval, although the analysis was performed also for the third recovery minute. Mean spatial QRS and T vectors were constructed by means of a mechanical vector analyzer.[15] The direction of the vectors is given in terms of azimuth (H°) and elevation (V°), and also the angle between the mean spatial QRS and T vectors (dA°) was obtained. The reference axis for the azimuth goes from left (0 degrees) to right (180 degrees) through the hypothetical center of the heart, dividing an anterior positive and a posterior negative hemisphere. The elevation is the angle between the vector and a perpendicular projection through the center; an increasing angle corresponds to an increasing elevation. The angle dA° is measured from the mean QRS vector to the mean T vector, a positive sign denoting clockwise rotation, and a negative sign denoting counterclockwise rotation. Magnitude is expressed in units of 0.1 millivolt.

SUBJECTS

The subjects were clinically healthy business and professional men, gainfully employed in the middle and upper income brackets, and long-time residents in the metropolitan Minneapolis-St. Paul area. At the time of this study the average age was 56 years (range 50 to 61 years). All were native-born Americans and, with the exception of a few men with some central or southern European

antecedents, their ancestry was from the British Isles, Scandinavia, Germany, or the Netherlands. All were sedentary or in work that demands no more physical effort than standing or walking around part of the day. They were selected at random, according to convenience of our time schedule, from about 230 similar men who have been seen in detailed test and measurement sessions annually here for seven years and who have continued to be free of signs of hypertension or other cardiovascular disease. Originally, these men and seventy others who are not now clinically healthy or have died, were selected from among 916 men who accepted our offer extended to 1,000 men to join a long-time research project. The names of almost all of the 1,000 men invited were provided by Minneapolis-St. Paul business firms in response to our request for cooperation by furnishing a list of permanent employees, aged 45 to 55 and presumed to be healthy, that the firms in question would authorize to join the project, and to take off a day a year for the purpose. A few men were invited because they hold prominent positions in the University of Minnesota or in the State. Since our capacity was 300, and the response was so complete, after rejections for physical defects, elimination was by lot except that some preference was given to fat or to thin men to be sure they were numerically represented well enough to allow statistical comparisons of extremes in relative body weight.

Relative body weight is expressed here as a percentage of the "standard" average for given age and height in the Medico-Actuarial Tables.[16] These were used, not as an accurate description of true United States averages, which are not known, but as a widely-used reference system, available everywhere, for expressing relative body weight. The total group was subdivided into a "normal" weight group of twenty-eight men (95 to 105 per cent standard weight), an "underweight" group of thirty-one men (below 95 per cent standard weight), and an "overweight" group of thirty-two men (over 105 per cent standard weight). The average relative weight for the underweight group was 87.0 per cent, and that of the overweight group was 113.7 per cent. The effect of absolute body weight was evaluated by comparing two subgroups of nearly identical relative body weight, as close to the relative weight of 100 per cent as possible, but significantly different in absolute body weight.

RESULTS

Total Group: Conventional ECG Items.—Table I shows the changes in conventional electrocardiographic items, in the total group of ninety-one men, after the step test (upper part) and after walking on the treadmill (lower part). The effect of relative body weight is balanced, since the number of underweight (<95 per cent of standard weight), normal weight (95 to 105 per cent standard weight), and overweight (>105 per cent standard weight) subjects is nearly identical. The step test produced highly significant changes in all items which does not agree with statements[4-6,7] that most electrocardiographic items do not change significantly in normal persons after this type of exercise. Although the differentiation between normal and abnormal does not necessarily depend on the magnitude or statistical significance of changes, the results suggest that some other items may have potential diagnostic value in addition to changes of the S-T segment and directional changes of the T wave.

TABLE I. CHANGES IN CONVENTIONAL ECG ITEMS IN NINETY-ONE NORMAL OLDER MEN AFTER A STEP TEST AND AFTER WALKING ON THE TREADMILL (3 M.P.H.; 5 PER CENT; 10 MINUTES)

	HEART RATE	S-T SEGMENT		AXIS (DEGREES)		AMPLITUDES				
		II	V_4	QRS	T	ΣQRS	ΣT	R_2	T_2	T_{V_4}
STEP TEST										
M	21.2	−0.4	−0.3	5.5	10.5	−1.8	−0.7	−0.4	−0.2	−1.3
S.D.	9.1	0.3	0.5	11.1	17.6	2.4	1.4	0.9	0.7	1.5
t	22.1*	10.5*	6.5*	4.7*	5.7*	7.3*	5.0*	4.5*	2.9†	8.1*
WALKING										
M	22.2	−0.2	—	5.4	13.5	−0.5	−0.8	0.1	−0.2	—
S.D.	9.1	0.2	—	13.4	16.1	3.1	1.5	0.9	0.9	—
t	22.8*	9.5*	—	3.7*	7.9*	1.6	4.9*	1.5	2.6†	—

M = means, S.D. = standard deviations, t = statistical significance of changes from zero.
*p = < 0.001.
†p = < 0.01.

The group is large enough to indicate the limits for clinically healthy men between 50 and 60 years. From the means and the standard deviations in Table I the "normal" 95 per cent limit for the S-T_2 depression is −1.0, and for depression of S-T_{V_4} is −1.3 (rounded to −1.5), which is greater than the limits suggested by Master,[4-6] but agrees well with the results of other authors.[10,11,18-23]

The changes of all items except the QRS amplitude (ΣQRS and R_2) are also highly significant after walking. Differences of the response between the step test and walking will be more specifically discussed in a later section.

Mean Spatial QRS and T Vectors.—Table II shows the changes of direction and magnitude of the mean QRS and T vectors in the total group of ninety-one men for the step test (upper part) and for walking (lower part), in terms of mean differences between rest and exercise (M), their standard deviations (S.D.), and the statistical significance of their deviations from zero evaluated by means of the t-test (rows one to three). The medians are shown in row four for comparison with the means (M). In view of the variability as expressed by the S.D., the differences between the means and the medians are minor, indicating only a relatively slight skewness of distribution. The use of the t-test, therefore, was justified, and the very high statistical significance of the changes in most items is certainly meaningful. There is a highly significant posterior rotation of both the QRS and T vectors (negative change of azimuth H°), and a highly significant decrease of their magnitude after the step test. The highly significant decrease of the elevation of the T vector corresponds to the right shift of the Einthoven T axis (Table I). On the other hand, the absence of a significant change of the angle (dA°) between the mean spatial QRS and T vectors is surprising, since the angle increases in clinical ventricular ischemia.

TABLE II. CHANGES IN DIRECTION AND MAGNITUDE OF SPATIAL MEAN QRS AND T VECTORS AFTER STEP TEST AND AFTER WALKING ON THE TREADMILL—MEDIANS, MEANS, AND STANDARD DEVIATIONS IN NINETY-ONE OLDER MEN

	QRS			T			
	H°	V°	MAGNITUDE	H°	V°	MAGNITUDE	dA°
STEP TEST							
M	−6.0	−2.4	−1.5	−2.4	−8.8	−0.7	1.7
S.D.	8.1	14.2	2.0	9.4	16.0	1.1	12.7
t	7.0*	1.6	7.4*	2.4†	5.3*	6.1*	.19
Median	−4.9	−2.7	−1.5	−3.3	−8.3	−0.6	2.7
Upper L	+9	+31	+1.5	+18	+18	+1.0	+25
Lower L	−28	−26	−6.3	−25	−41	−3.7	−28
WALKING							
M	−5.0	−5.7	−0.7	0.5	−10.6	−0.7	−0.7
S.D.	7.1	13.4	1.8	11.8	15.5	1.2	15.9
t	6.6*	3.9*	3.4†	0.3	6.3*	5.0*	0.4
Median	−4.3	−5.5	−0.8	−1.1	−9.4	−0.6	0.0
Upper L	+9	+14	+3.0	+22	+14	+1.3	+29
Lower L	−20	−30	−3.9	−20	−43	−2.8	−39

t = Significance from zero expressed by t-test.
L = Rounded limits calculated from the percentile distribution, for 95 per cent of "normal" population, of which the group is a representative sample.
*p = <0.001.
†p = <0.01.

The significant changes in five out of seven items of spatial vector analysis are suggestive of potential diagnostic value, and therefore, the rounded upper and lower limits for 95 per cent of a population of healthy older men, of which this group is a representative sample are given in rows five and six. The limits were calculated from the percentile distribution. To the best of our knowledge, these are the first normal standards for postexercise changes of the spatial vectors. The lower part of Table II shows the changes of the mean spatial QRS and T vectors after walking on the treadmill. Five out of seven items show highly significant changes. There are some differences between the changes after walking and after the step test, but the range limits are quite similar in most items. It is interesting that the variability as shown by the standard deviations is of the same order of magnitude as the resting repeat variability.[25]

Effect of Relative Body Weight.—The total group was subdivided into subgroups of thirty-one underweight, twenty-eight normal weight, and thirty-two overweight men. Tables III and IV show the changes of conventional electrocardiographic items after the step test and after walking, respectively, in these relative body weight groups. The significance of the differences in the response between the underweight and the overweight groups was evaluated by means of the t-test. Significant t values are given and absence of statistical significance

is expressed by the symbol "n.s." The greater right axis shift and smaller decreases of the T wave in V_4 in the overweight group after the step test was statistically significant at the 5 per cent level. The difference in the right axis shift is large enough to merit consideration in normal standards. From the frequency distribution, a tentative preliminary normal limit of +25 degrees is suggested for the right shift of the T axis in the underweight group, and of +45 degrees in the overweight and normal weight groups, and a left T-axis shift of −15 degrees for the underweight group, and −20 degrees for the overweight group. The greater decrease of ΣQRS in the overweight group was significant only at the 10 per cent level. Most items, including the S-T segment, do not show significant differences between the weight groups, and this is true also for walking on the treadmill (Table IV), where only the change of ΣQRS is significantly different between the overweight and the underweight group. This is surprising, since most electrocardiographic items show significant relative body weight trends in the resting electrocardiogram.[2]

TABLE III. CHANGES IN CONVENTIONAL ECG ITEMS AFTER STEP TEST IN THIRTY-ONE UNDERWEIGHT, TWENTY-EIGHT NORMAL WEIGHT, AND THIRTY-TWO OVERWEIGHT NORMAL OLDER MEN

	HEART RATE	S-T SEGMENT		AXIS (DEGREES)		ΣQRS	ΣT	R_2	T_2	T_{V_4}
		II	V_4	QRS	T					
Underweight										
M	21.5	−0.4	−0.4	3.9	4.8	−1.4	−0.5	−0.6	−0.3	−1.7
S.D.	11.7	0.3	0.6	11.9	10.7	2.2	1.3	1.0	0.8	1.7
Normal Weight										
M	20.1	−0.4	−0.2	6.2	12.6	−1.6	−1.2	−0.5	−0.3	−1.4
S.D.	5.9	0.4	0.5	9.8	22.0	2.2	1.6	0.8	0.7	1.3
Overweight										
M	21.9	−0.4	−0.3	6.3	14.3	−2.4	−0.5	−0.1	−0.2	−0.8
S.D.	8.8	0.4	0.4	11.7	17.7	2.7	1.2	0.7	0.6	1.3
Significance, Underweight versus Overweight										
△	+0.4	0.0	+0.1	+2.4	+8.5	−1.0	0.0	+0.5	+0.1	+0.9
t	n.s.	n.s.	n.s.	n.s.	2.6‡	1.7#	n.s.	2.0‡	n.s.	2.4*

The statistical significance of the mean differences △ between high and low absolute body weight evaluated with the t-test.
‡p = <0.05.
#p = <0.1.

TABLE IV. CHANGES IN CONVENTIONAL ECG ITEMS IN UNDERWEIGHT, NORMAL WEIGHT, AND OVERWEIGHT NORMAL OLDER MEN AFTER WALKING ON THE TREADMILL

	HEART RATE	S-T_2	AXIS		AMPLITUDES			
			QRS (DEGREES)	T (DEGREES)	ΣQRS	ΣT	R_2	T_2
Underweight								
M	22.2	−0.3	4.3	12.6	0.2	−0.5	0.1	−0.2
S.D.	10.7	0.3	11.7	14.0	3.0	1.4	0.9	0.9
Normal Weight								
M	18.7	−0.2	2.5	12.0	−0.3	−1.0	0.4	−0.2
S.D.	5.4	0.2	17.1	14.8	3.1	2.0	1.1	1.0
Overweight								
M	25.2	−0.2	8.8	15.6	−1.4	−1.0	0.0	−0.3
S.D.	9.1	0.2	11.0	19.0	3.2	1.2	0.9	0.7
Significance, Underweight versus Overweight								
Δ	+2.9	+0.05	+4.5	+3.0	−1.6	−0.5	0.1	−0.1
t	n.s.	n.s.	n.s.	n.s.	2.1‡	n.s.	n.s.	n.s.

‡p = <0.05.

The mean spatial QRS and T vectors did not show significant differences between the underweight and overweight groups after the step test; however, the greater change of T-V° in the overweight group (−10.7 degrees) than that in the underweight group (−7.6 degrees) parallels the greater T-axis shift to the right.

There were, however, significant differences in the magnitude of the QRS vector (greater decrease in the overweight group) and in the angle dA° between the QRS and T vectors (increase in the overweight group, decrease in the underweight group) after walking on the treadmill (Table V). The different direction of the change of T-H° was significant only at the 10 per cent level. While in regard to spatial vectors walking differentiates overweight and underweight better than the step test, the effect of relative body weight is less pronounced than it is in resting condition.[2]

Effect of Absolute Body Weight.—In order to differentiate between the effect of relative and absolute body weight, two groups with high and low absolute body weight were selected from the total group, matched as closely as possible in regard to a normal relative weight of 100 per cent. For the step test, absolute weight groups of twenty-four (heavy) and nineteen (light weight) men were obtained, and for walking twenty-four (heavy) and twenty (light weight) men. The small difference between the relative weights of both groups, and between normal relative weight of 100 per cent and the relative weight of these groups

TABLE V. CHANGES OF SPATIAL MEAN QRS AND T VECTORS IN UNDERWEIGHT, NORMAL WEIGHT, AND OVERWEIGHT OLDER MEN AFTER WALKING ON THE TREADMILL

	QRS			T			
	H°	V°	MAGNITUDE	H°	V°	MAGNITUDE	dA°
Underweight							
M	−5.5	−6.2	0.0	−2.0	−11.0	−0.6	−5.9
S.D.	5.7	16.3	1.7	8.9	13.1	1.4	15.3
Normal Weight							
M	−6.0	−2.9	−0.6	0.0	−10.8	−0.8	5.6
S.D.	5.6	13.6	1.8	11.0	17.4	1.5	14.1
Overweight							
M	−3.8	−7.5	−1.3	+3.3	−10.0	−0.6	+3.2
S.D.	9.1	9.4	1.5	14.5	16.5	0.8	16.1
Significance of Differences: Overweight versus Underweight							
Δ	+1.7	−1.3	−1.3	+5.3	+1.0	0.0	+9.1
t	n.s.	n.s.	3.0†	1.7#	n.s.	n.s.	2.2‡

†p = <0.01.
‡p = <0.05.
#p = <0.1.

was statistically not significant. On the other hand, the difference of the absolute weight (10.8 and 9.2 kilograms, respectively) was very highly significant; actually, there was no overlapping of individual values.

In Table VI, the ECG changes of the high and low weight group are compared after the step test, and in Table VII after treadmill walking. Only one conventional item (T_{V_4}) and one item of vector analysis (QRS-H°) showed a statistically significant differentiation between the weight groups.

No conventional or vectorial ECG item showed a significant difference between the weight groups after walking.

In summary, the relative body weight groups showed differences at a level of expectancy of 10 per cent or better in a total of seven items (both types of exercise and conventional and vectorial items), as compared to a total of two items in the absolute body weight groups. The relative body weight, therefore, appears to be the more important variable, which might have been expected, but there are only very few items where consideration even of the relative body weight appears to be really worthwhile. No corrections for the absolute body weight are suggested at the present time. The differences of −0.9 for T_{V_4} and of 5.2 degrees for QRS-H° after the step test, although statistically significant, are relatively small as compared to the interindividual and repeat variability.

TABLE VI. POSTEXERCISE (STEP-TEST) CHANGES OF CONVENTIONAL AND VECTORIAL ECG ITEMS IN TWO GROUPS OF OLDER MEN WITH HIGH AND WITH LOW ABSOLUTE BODY WEIGHT, AT NEARLY IDENTICAL RELATIVE WEIGHT

CONVENTIONAL ECG

GROUP	NO.	% RELATIVE WEIGHT	ABSOLUTE WEIGHT	(KG.)	HEART RATE		$S\text{-}T_2$		$S\text{-}T_{V_4}$		R_2		T AXIS		T_{V_4}	
		M	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
H	24	98.1	78.5	3.8	19.9	6.2	−0.4	0.3	−0.2	0.4	−0.6	0.9	12.0	21.1	−1.9	1.2
L	19	97.7	69.4	3.8	19.8	6.3	−0.2	0.3	−0.3	0.6	−0.6	1.0	9.1	17.4	−0.9	1.3
Δ		0.4	9.2		0.1		0.2		0.1		0.02		3.9		1.0	
t			7.84*		0.02		1.42		0.08		0.06		0.5		2.66†	

MEAN SPATIAL VECTORS

	NO.	QRS						T							
		H		V		MAGNITUDE		H		V		MAGNITUDE		dA°	
		M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
H	24	−3.3	6.9	0.2	17.6	−1.6	2.4	−1.6	6.4	−8.6	19.8	−0.9	1.1	1.5	13.2
L	19	−8.6	7.5	−6.6	11.6	−1.4	1.4	+0.9	7.3	−6.8	17.4	−0.7	1.4	2.8	12.6
Δ		5.2		6.8		0.2		2.5		1.8		0.2		1.3	
t		2.38‡		1.46		0.40		1.20		0.31		0.42		0.35	

H = high absolute body weight; L = low absolute body weight.
*p = <0.001.
†p = <0.01.
‡p = <0.05.

TABLE VII. POSTEXERCISE (WALKING ON TREADMILL) CHANGES OF CONVENTIONAL AND VECTORIAL ECG ITEMS IN TWO GROUPS OF NORMAL OLDER MEN WITH HIGH AND LOW ABSOLUTE BODY WEIGHT, AT NEARLY IDENTICAL RELATIVE BODY WEIGHT

CONVENTIONAL

GROUP	NO.	% RELATIVE BODY WEIGHT	ABSOLUTE BODY WEIGHT		HEART RATE		$S\text{-}T_2$		R_2		T AXIS	
			M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
H	24	100.1	80.6	4.9	19.2	6.2	−0.3	0.2	0.2	1.1	14.0	14.5
L	20	98.6	69.8	3.6	20.9	9.0	−0.2	0.3	0.3	1.2	12.6	15.0
Δ		1.5	10.8		1.7		0.1		0.1		1.4	
t			8.2*		0.70		1.7		0.20		0.3	

SPATIAL VECTORS

GROUP	NO.	QRS						T							
		H°		V°		MAGNITUDE		H°		V°		MAGNITUDE		dA°	
		M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.	M	S.D.
H	24	−5.0	5.4	−6.0	17.2	−0.3	2.0	4.4	14.7	−12.0	17.8	−0.5	0.7	1.6	15.6
L	20	6.2	9.2	−1.8	15.5	−0.1	1.5	0.5	11.1	−8.5	9.9	−1.0	0.9	5.7	15.8
Δ		1.2		4.2		0.2		3.9		3.5		0.5		4.1	
t		0.50		0.80		0.29		0.96		0.75		1.3		0.84	

*p = <0.001.

The results show that there is no basis for the absolute body weight gradation in Master's standard procedure. It will be noted that the heart rate, on which Master's procedure is largely based, is identical in the low and high absolute weight group, in corroboration of more extensive data published previously.[26]

Comparison of Step Test and Walking.—Three out of eight conventional ECG items and two out of seven vectorial ECG items show highly significant differences in the response between the step test and walking (Table VIII). The difference in the change of the T axis and QRS—V° does not quite reach the 5 per cent level of statistical significance. Step test and walking, therefore, are not equivalent. If, however, only the S-T segment is evaluated, as is usually the case, the difference is quite small.

TABLE VIII. DIFFERENCES IN THE POSTEXERCISE CHANGES OF CONVENTIONAL AND VECTORIAL ECG ITEMS BETWEEN STEP TEST AND WALKING IN NINETY-ONE OLDER MEN, AND THEIR STATISTICAL SIGNIFICANCE (T-TEST)

CONVENTIONAL ECG ITEMS

TEST	HEART RATE	S-T_2	QRS AXIS	T AXIS	ΣQRS	ΣT	R_2	T_2
Walk	21.2	−0.4	5.5	10.5	−1.8	−0.7	−0.4	−0.2
Step	22.2	−0.2	5.4	13.5	−0.5	−0.8	0.1	0.2
Δ	−1.0	−0.2	+0.1	−3.1	−1.3	+0.1	−0.5	0.0
t	0.7	3.75*	0.1	1.9#	4.2*	0.4	4.7*	0.0

SPATIAL VECTORS

	QRS			T			
	H°	V°	MAGNITUDE	H°	V°	MAGNITUDE	dA°
Walk	−5.0	−5.7	−0.7	0.5	−10.6	−0.7	−0.7
Step	−6.0	−2.4	−1.5	−2.4	−8.8	−0.7	1.7
Δ	−0.9	+3.3	−0.8	−2.9	+1.8	0.0	+2.4
t	0.8	1.7#	3.7*	2.5†	0.8	0.3	1.1

*p = <0.001.
†p = <0.01.
#p = <0.1.

The significant differences between the step test and walking do not show superiority or inferiority of one or the other type of exercise in regard to the separation between normal subjects and patients, since most of the items listed in Table VIII have not yet been statistically evaluated for this purpose. There are, however, some general considerations pertinent to this question. The typical abnormal response in patients with coronary insufficiency will occur whenever the oxygen supply becomes inadequate for the myocardial oxygen requirement. This explains why various types of exercise have been suggested and quite successfully used by various authors.[1] We were not able to reproduce the typical

postexercise ischemia pattern of coronary patients in thirty young men subjected to very severe anaerobic exercise (running at 7 miles per hour on a 10 per cent grade). In these normal men the most impressive changes were a tremendous increase of the T wave, anterior rotation of T-H°, and posterior rotation of QRS-H°. The abnormal response in patients with coronary insufficiency, therefore, is not only quantitatively different (i.e., it is not reproducible in normal subjects by very severe exercise), but it is also qualitatively different. Therefore, for the grossly abnormal response no quantitative normal standards are needed, nor, in agreement with Scherf and Schaffer,[1] does the type of exercise seem to be of primary importance. However, the response to exercise is not always frankly abnormal in coronary heart disease and, therefore, normal standards, including a standardized type of exercise, are needed for the differentiation of some patients from normal persons.

There seems to be a critical level of exercise in the patient with coronary insufficiency, below which the response is normal, and above which it is abnormal. This level varies widely not only in different patients, but also in the same patient. The proper design of an exercise tolerance test would obviously be a level of the load which will elicit an abnormal response in the majority of patients, but still with a minimum of risk. Although all types of exercise tests which have been used for patients are comparatively safe, it should be recognized that the risk cannot be entirely eliminated in a procedure which depends for its efficacy on producing coronary insufficiency.* The critical level does not depend on the level of inadequacy of coronary blood supply alone, but also on its duration. It is possible, therefore, and probably safer to produce the critical level by extending the duration of moderate work rather than by increasing the intensity of the work load in a test of short duration, because of the larger oxygen debt in the latter procedure. For evaluation of this aspect in the two types of exercise under consideration, the oxygen consumption was measured in a 24-year-old normal man weighing 132 pounds, both at the steady state in walking at 3 miles per hour on a 5 per cent grade and in stepping up and down. The rate for the step test, as determined from Master's tables[4] for this subject, was 300 inches lift per minute. The expired air was collected during the tenth to thirteenth minute of walking and fourth to seventh minute of stepping. For the level of oxygen requirement, which is the best basis for determination of the physiologic load, the measurement at a steady state is most reliable, and it is irrelevant for this purpose that the duration of both exercise tests is actually shorter. The oxygen consumption during walking was 1,175 c.c. per minute, which agrees well with results obtained in a larger material in our laboratory.[13] The oxygen consumption during stepping was 1,780 c.c. per minute, or 51 per cent higher. While the absolute oxygen consumption characterizes the total metabolic and circulatory load, for the characterization of the severity of exercise the excess oxygen (over the level of the basal metabolic rate) is pertinent. It was 945 c.c. per minute for walking, and 1,550 c.c. for stepping,

*Precipitation of myocardial infarction by Master's two-step test was recently suggested by Grossman and Grossman.[47]

or 64 per cent higher. The step test, therefore, is definitely the more severe exercise. For this reason, and also because of considerable muscular fatigue, a prolongation of the step test over three minutes is not advisable. We have used both types of exercise in a large number of patients with heart disease. In our experience, walking produces at least as many abnormal responses, and probably more than the step test. Walking at moderate speed, therefore, seems to be preferable as an exercise test.

COMMENT

Validity and Significance of Normal Standards for the Exercise Test.—The results presented above may serve as a basis for discussion of the validity of normal electrocardiographic exercise tolerance standards for separation of normal persons and cardiac patients. Although the exercise test has been successfully used in various pathologic conditions[1] the application to patients with coronary artery disease is by far the most important, because of the lack of objective criteria in a substantial number of such patients. Since Master's two-step exercise test is one of the most commonly used, much discussion is concerned with the validity of Master's standards. The availability of reliable normal standards was, indeed,[4-6,27,28] stressed as an important advantage of this test. These standards go back to older material,[7] based on the recovery of blood pressure and pulse rate after a step exercise. Discussion of their validity should include a critical evaluation of this older material, which has not been done in the previous electrocardiographic literature.

In the commonly accepted practice of physical fitness testing, the rate, load, and duration of work is kept constant for all individuals, and corrections are made for height, weight, age, and sex, dependent on the response of the various physiologic functions to exercise observed in these different categories of normal population.[29] The advantage of this procedure is a rigid standardization of work in regard to rate, speed, duration, and load (in types of locomotion relative to the body weight). The physiologic load, however, would be not equal for different individuals.

In contrast, Master and Oppenheimer[7] tried to provide a physiologically equivalent load for all individuals, taking into account age, height, sex, and particularly absolute body weight, since "the heavier the patient, the more foot-pounds of energy are consumed in walking the steps."[6] With this procedure, the physical amount of work (number of ascents) is different for different individuals according to age, body weight, and sex.

However, the underlying concept of a parallelism of physiologic load and body weight is an oversimplification. The absolute energy expenditure increases with body weight in locomotion, but the calorie expenditure per unit of body weight and unit distance, which is a better index of the physiologic load, shows comparatively little interindividual variability.[13] While the amount of work in locomotion increases with the body weight, muscle mass and heart size also increase with the body weight, and it is not certain, a priori, that for the same distance the physiologic load or the recovery speed (which was used by Master

as an inverse index of the physiologic load) will be greater in a heavier subject with similar body composition. If this concept is applied to the comparison of animals of much different size—which is a legitimate procedure in testing the validity of general physiologic concepts—the expected recovery time after a run over the same distance would be absurdly long in a horse as compared to a dog. In general, the physiologic mechanisms are adapted to the transport of the body weight. In work not involving locomotion, such as lifting loads, the larger and therefore heavier subject has a definite advantage.[30]

The determination of the physiologic load in Master's and Oppenheimer's series was based on the maximum number of ascents "which could be accomplished without delaying the return to resting circulatory conditions beyond the prescribed two minutes." Both pulse rate and blood pressure were used to standardize the test for a duration of one and one-half minutes. The relationship between work load and pulse rate is poor in the initial phase of exercise,[12] and therefore large variability in the individual responses should be expected for so short a work period. This is actually shown in the scatter diagrams in Master's and Oppenheimer's original communication.[7] The data were obtained in fifty-nine men and fifty-six women, of varying weights and heights, and ranging in age from 10 to 74 years. For the large range of the variables involved the group was too small for predicting reliable normal standards, particularly in view of the large variability of pulse rate and blood pressure, but the corrections of these standards, based on substantially enlarged material, were only minor.[8] The tables show the equivalent number of ascents for absolute body weight and age, while in the first communication the equivalent load was given in terms of foot-pounds for weight and age, with a correction for the height, which was dropped later.

In our material, there was no effect of the absolute body weight on the excess pulse rate in the first and third recovery minute after the step test, corroborating earlier results by Elbel and Holmer,[31] and by Buskirk and associates.[26]

However, Master used the blood pressure recovery as well as that of the pulse rate, so that our series and that of Elbel and Holmer are not quite comparable to his material. However, since the pulse rate is more closely related to the work load than the blood pressure, it is very unlikely that the blood pressure will show a better correlation.*

Master and associates found, in 1952,[32] that in thirty out of one hundred and eighty-seven normal subjects with a normal electrocardiographic response after the two-step test, the recovery of the heart rate was not complete within five minutes. It is clear that a substantial number of subjects had not recovered the pulse rate two minutes after the single-step test, which was the original

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*That the increase of the pulse rate and its slower recovery with increasing body weight in Master's material might be a concealed effect of the fat content, is suggested by recent experiments in our laboratory[26] (Buskirk and associates). The excess pulse rate during walking and recovery was most highly correlated with the per cent fat content of the body (densitometrically determined), less well correlated with the relative body weight, and least with absolute body weight. In the smaller group of this series, the excess heart rate after walking is also higher in the overweight group, but the difference does not reach the level of statistical significance. Master and associates[7,8] did not differentiate between absolute and relative body weight, but it is very likely that their heavier subjects tended to be more obese as well.

criterion for standardization. This series was recently enlarged (Wener and associates[17]) with similar results. Among 286 normal subjects with a normal electrocardiographic response, the pulse rate or blood pressure had not recovered within five minutes after the single-step test in 14 per cent and in 24 per cent after the double-step test. This means that Master and his associates were unable to reproduce the results, on which their standards are based, or that they accept the idea that a fourth of any sample of clinically healthy subjects must be judged "abnormal."

While Master's gradation of the exercise test according to body weight does not seem to have a valid basis—both in regard to pulse recovery and electrocardiographic changes—the large material investigated with this testing procedure is still valuable because it provides a background for the differentiation between normal subjects and patients by the two-step test, as used by Master. However, this material cannot be considered as proof for the value of the gradation of exercise according to age and weight.

According to the latest (and largest) material (311 subjects) reported from Master's laboratory,[17] the depression of the S-T segment exceeded 0.5 mm. only in 3.2 per cent in the single-step test, and in 7.1 per cent in the double-step test, T wave changes were minimal, and no abnormal T inversion occurred, nor were there significant changes in other electrocardiographic items. This seems to be a good basis for differentiation between normal and abnormal, but the majority of other investigators[10,11,18-23] have found greater changes, particularly of the S-T segment, and this is true also for this series.

In spite of this evidence, Master did not change his limits because this would produce too many false negative tests. On the other hand, Master's liberal limits for a normal response increase the number of false abnormal responses to such an extent that the practical utility is questionable[20,21,33,34]; in any case it is far higher than the 6 to 8 per cent of false abnormal responses reported by Master and associates.[17,27] However, Master and associates,[35] suggested that a false abnormal response indicating a functional coronary insufficiency is due to emotional or anxiety states and could be eliminated by ergotamine tartrate. Master accepted Nordenfelt's[35a] view that ergotamine converts the abnormal response to normal in neurotic patients, but not in patients with organic heart disease. But in a group of five "neurotic" patients used to demonstrate this thesis, two had typical and one had an atypical history of angina pectoris. The presence of coronary artery disease, therefore, could not be safely excluded in some patients of this very small group. In a comparable group of five patients with definite coronary disease, no analysis of their emotional and psychologic status was made. Furthermore, the age range of the groups with "functional" and with organic heart disease was very different (26 to 40 years versus 44 to 76 years). There was no independent evidence that the separation of these groups by means of the ergotamine effect was correct. Moreover, it is not true that ergotamine has no effect on patients with definite heart disease. Ergotamine tartrate may normalize the abnormal T wave in left ventricular strain[36] or in myocardial infarct.[37] Pordy and associates[38] later replaced ergotamine tartrate with dihydroergocornine because of the side effects

of ergotamine. However, the same objections (lack of independent controls) can be made also against the series of Pordy and associates and dihydroergocornine is also not free of side effects. It was discontinued for this reason and was replaced by Hydergin (Solomon[39]). Studying the effects of Hydergin (CCK 179), this author concludes that cardiac effects of ergot derivatives are "still shrouded in deep mystery." The diagnostic use of ergotamine, dihydroergocornine, or Hydergin for differentiation between organic and functional coronary insufficiency appears to have little justification at this time.

Leeds and Kroopf[33] found an abnormal response to Master's step test in six out of sixty-nine normal women (8.7 per cent) under 35 years of age, but coronary heart disease is rare in such a group, and there was no evidence of neurocirculatory asthenia, an unusual emotional state or any organic cause to account for the results. Also, in their men with false positive tests, there was no evidence of an anxiety state, and some of our own observations are confirmatory. It seems, therefore, that in a substantial number of false "abnormal" responses the cause is neither known nor, at present, is it knowable.

Master and associates, however, seem to stress negative tests rather than positive tests; a false negative test is stated to occur in only about 5 per cent of patients with coronary heart disease, and therefore, a negative test practically excludes organic coronary disease.[6,40]

Obviously, the high frequency of false negative tests with the single-step test was the reason for the introduction of the double-step test. Further increase of the duration of the step test would most likely produce a positive response in at least some of the patients with false negative tests.

Be this as it may, the emphasis on a negative rather than on a positive test is a very unusual statistical evaluation. It should be based on the distribution of responses in an abnormal population (i.e., of patients with coronary disease) rather than on the distribution among normal persons. In a recent study of the distribution of Q_3 and twelve related ECG items, there was a wide overlapping between the distributions of patients with posterior wall myocardial infarction and of a normal population.[41] A wide overlap should also be expected in other electrocardiographic items, particularly when the group of coronary patients is less rigidly defined. Unfortunately, the distribution of responses to exercise tolerance tests in an abnormal population is virtually unknown because of the lack of independent criteria to characterize such groups. If the value of the exercise response is to be tested, obviously the results of the exercise response itself cannot be used as a proof of the validity for the separation of the groups. The only coronary patients where an objective and independent differentiation is possible are those with a rather complete history of myocardial infarction, because in these patients the presence of coronary disease is unquestionable. However, Master and associates found in patients with healed myocardial infarction that the exercise test was quite often negative.[42] This is, indeed, hard to reconcile with the statement that a negative test practically rules out coronary disease,[6,27,40] or that it even might detect malingering.[40] The percentage of false negative tests will depend on the severity and duration of the exercise, and on the composition of the population group examined. It is

not surprising, therefore, that other authors found a higher incidence of false negative tests.[18,19,33] Leeds and Kroopf,[33] for instance, found the two-step test normal in sixteen men with abnormal resting electrocardiograms. In their large group of apparently normal persons in a working population, more abnormal cases were detected with the resting electrocardiogram than with Master's two-step test. This, however, does not necessarily diminish the diagnostic value of the exercise test, since this is an additional diagnostic procedure and might discover abnormalities that would be missed without it.

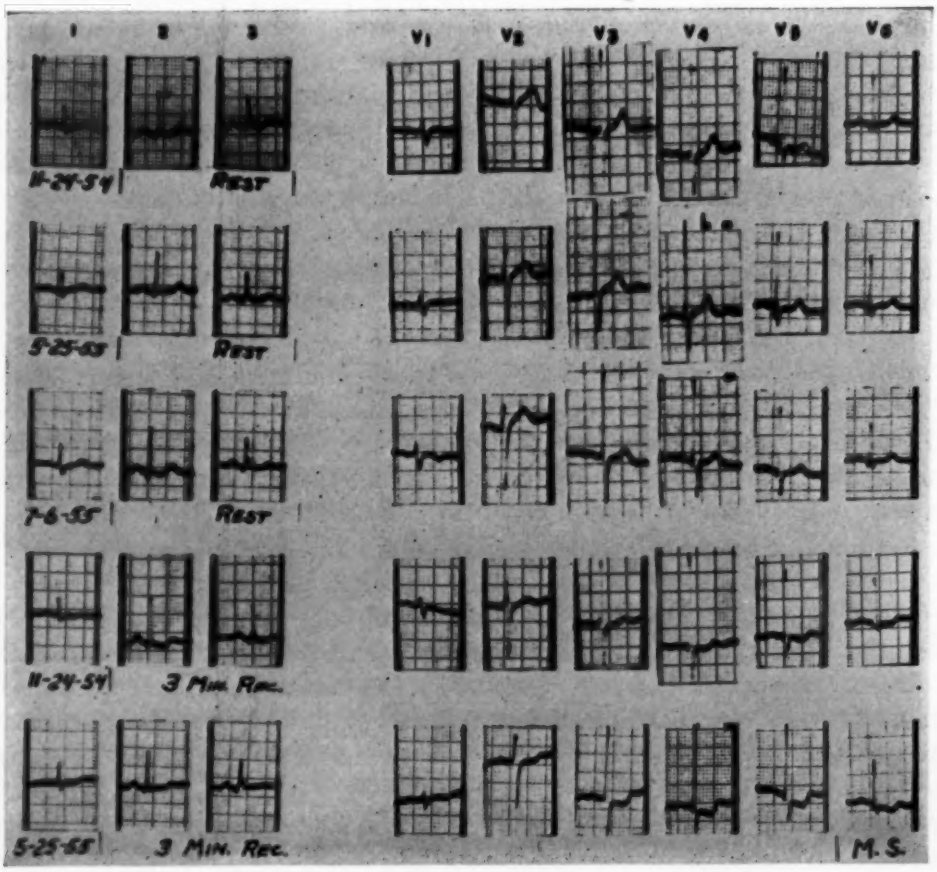

Fig. 1.—S. M., age 43 years. Resting ECG's November 24, May 25, and July 6 are normal (first three rows). Exercise test on November 24, walking on the treadmill, 3 m.p.h., 5 per cent grade, was terminated after one minute and fifteen seconds because of chest pain. The ECG shows the typical pattern of subendocardial ischemia still in the fourth recovery minute (fourth row). Six months later (May 25), the tolerance for the same type of exercise was reduced to one minute, and the S-T depression in the precordial leads in the fourth recovery minute was more pronounced. During the first recovery minute, the S-T depression was equally severe on both occasions; in this case the deterioration was shown in the prolongation of the recovery rather than in the immediate response.

The question of retrospective evaluation of the diagnostic significance by means of follow-up studies[28] is outside of the scope of this article, but a brief general comment may be made. The exercise test is a valuable additional tool in the analysis of the state of the patient at the time of investigation. A larger percentage of patients with positive exercise tests should be expected to develop

arteriosclerotic heart disease than among patients with negative tests. The higher mortality in patients with abnormal exercise tests shows its usefulness for group prognosis, but the prognostic value for an individual patient is very limited. We have several middle-aged men under observation who have had an abnormal exercise test for four years, but they still fail to show any evidence of clinical coronary disease. Even if this ultimately develops, the relationship to the abnormal exercise test is not certain. We have also confirmed Durham's[43] observation that the exercise test may be normal a few days or weeks before myocardial infarction. Such observations show the limitations to the prognostic evaluation that can be made from the two-step test.

On the other hand, in one of our patients with typical, frequent attacks of angina pectoris, the resting ECG was normal over a period of seven months, the last one taken three weeks before death from coronary thrombosis, while the exercise test was abnormal and showed deterioration in the precordial leads (Fig. 1).

SUGGESTIONS FOR TESTING PROCEDURE AND NORMAL STANDARDS

A. *Type of Exercise.*—From general considerations, as discussed before, walking on the treadmill appears to be the preferable exercise test. Our speed of 3 miles per hour on a 5 per cent grade has been convenient for all normal subjects and for most patients up to the age of 60 years. In our experience, a slight grade and a relatively slow speed is easier to manage than level walking at a faster speed involving the same level of energy expenditure. For some patients, and probably for some normal old people, the speed of 3 miles per hour may be somewhat fast, and standards with a slower speed (about 2 miles per hour) will be necessary. A speed of 2.6 miles per hour, zero grade, was used by Yu and associates, but the group of twenty-five normal subjects was too small to provide reliable standards, and the authors concentrated mainly on the changes of the Q-T interval.

While there were significant differences in various ECG items between walking and the step test, the difference in the S-T depression, although statistically significant, was quite small. For practical reasons, the step test is a suitable substitute. It should be standardized as to total lift per minute and duration. The total lift depends on the height of the steps and the rate. In our series, the total lift was 228 inches per minute with nineteen ascents. This would correspond to about twenty-five ascents with a step height of 9 inches. The rate should be controlled by a metronome, and the total duration (two and one-half minutes) by a stop watch. It is suggested to replace Master's two-step by a one-step exercise, doubling the number of ascents, because a one-step exercise is simpler to perform.

There is no justification for a gradation of the exercise according to the absolute body weight. While six out of eighteen electrocardiographic items showed statistically significant age differences between a group of young men and a group of older men after walking, it is much easier to correct for the differences in the standards after an identical exercise than to attempt to equalize the load. While no precise information on electrocardiographic age trends for

the step test is yet available, the results from walking suggest that the age gradation in Master's procedure is too large. It is suggested, therefore, to use the same number of ascents, rate, and duration for all individuals. That the gradation of exercise according to weight and age is not necessary, has actually been shown by Master and associates[40] who introduced the double two-step without changing the electrocardiographic criteria.

B. *Electrocardiographic Evaluation.*—Since in the typical abnormal response in coronary insufficiency S-T depression and T-wave inversion are the most impressive changes, attention has been largely focussed on these items. The results of this study suggest it may be desirable to evaluate other items in addition, and for this reason the normal limits for postexercise changes of the spatial QRS and T vectors were given. Schellong and Lüderitz[45] claim that minute changes of the QRS interval, measured in high-speed records (150 mm. per second) have greater diagnostic significance than S-T and T-wave changes. However, in our material (direct-writer and 25 mm. per second film transport) there was no significant change in the QRS interval.

Changes of the Q-T interval were evaluated by Yu and associates.[44] Although there were significant differences between relatively small groups of normal subjects and patients, the situation is very complex. Many different equations have been suggested for the relationship between heart rate and Q-T interval in the resting condition, and this in itself suggests their limitations. None of these equations is applicable to the tachycardia of exercise. The adaptation of Q-T to the heart rate is a slow process. For instance, in premature auricular beats the Q-T interval is, as a rule, the same as in the regular beats. In our semistarvation experiment,[46] the Q-T changes followed the changes of the heart rate with a delay of several weeks. The change of the Q-T interval during a steady state of exercise will depend on the duration of exercise, the absolute level as well as the increase of the heart rate in exercise, and the level of the resting heart rate. The situation during the initial phase of exercise, with rapidly rising heart rate, or in the recovery with rapidly falling heart rate, is even more complicated. While the results of Yu and associates are interesting and encouraging for further exploration, diagnostic application appears to be still in the tentative phase.

SUMMARY

1. Moderate exercise (walking on the treadmill and stepping up and down) produced statistically significant changes of most electrocardiographic items (both conventional and spatial vectors) in ninety-one middle-aged normal men.

2. Upper and lower limits of the changes of mean spatial QRS and T vectors are presented for both types of exercise for 95 per cent of a population of healthy older men, of which this group is a representative sample.

3. There were significant differences in the postexercise changes of several conventional and vectorial electrocardiographic items between an overweight and an underweight group, but the effect of relative body weight on the exercise electrocardiogram was less pronounced than the effect on the resting electrocardiogram.

4. Absolute body weight is an even less important functional variable than relative body weight and need not be considered in normal standards for the exercise test.

5. Three out of eight conventional electrocardiographic items and two out of seven vectorial electrocardiographic items showed statistically highly significant differences in the response between the step test and walking.

6. The validity of normal standards for the exercise tolerance test is critically discussed, and suggestions for the clinical application of exercise tests are made.

SUMMARIO IN INTERLINGUA

1. Exercitios moderate (marchar al ambulator rolante e montar e dismontar grados) resultava in statisticamente significative alterationes del majoritate del elementos electrocardiographic (e conventional e spatio-vectorial) in novanta-un normal homines de etate medie.

2. Le limites superior e inferior del alterationes del vectores spatial median QRS e T es presentate sub le conditiones de ambe typos de exercitio pro 95 pro cento de un population de normal homines de etates plus avantiate pro le quales le presente gruppo functiona como un specimen representative.

3. Esseva notate differentias significative inter duo gruppos a peso infra- e a peso supra-normal in le alterationes occurrente post le exercitios in plure elementos electrocardiographic conventional e vectorial, sed le effecto del relative peso corporee super le electrocardiogramma post exercitio esseva minus pronunciate que super le electrocardiogramma in stato de reposo.

4. Le absolute peso corporee representa un variabile functional ancora plus negligibile que le relative peso corporee. Il non es necessari prender lo in consideration in le establimento de standards normal pro le test a exercitio.

5. Tres ex octo elementos del electrocardiogrammas conventional e duo ex septe elementos del electrocardiogrammas vectorial monstrava statisticamente significativissime differentias le test a ambulation e le test a montar grados.

6. Es presentate un discussion critic del validitate de standards normal pro le test a toleration de exercitio. Proponimentos es facite pro le application clinic de tests a exercitio.

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THE EFFECT OF A GANGLIONIC BLOCKING AGENT (HEXAMETHONIUM) ON RENAL FUNCTION AND ON EXCRETION OF WATER AND ELECTROLYTES IN HYPERTENSION AND IN CONGESTIVE HEART FAILURE

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NUMEROUS clinical and experimental studies carried out during the last few years have shown that ganglionic blocking agents exert a marked effect on renal hemodynamics. During the hypotensive phase following the administration of such drugs as tetraethylammonium salts and penta- and hexamethonium compounds, pronounced reduction of the glomerular filtration rate (GFR) has been observed. For renal plasma flow (RPF) smaller decreases, and even rises have been reported.[1-4]

Retention of water and salt, caused by reduction in renal function, has been implicated in the mechanism of edema formation of congestive heart failure.[5-8] Therefore, a further reduction in the low filtration rate obtained in edematous cardiac patients due to ganglionic blocking agents might be expected to increase further the retention of water and salt. Actually, some recent observations indicate that, in patients with borderline heart failure, fluid retention can be precipitated by these drugs.[9] On the other hand, it has been claimed that the therapeutic administration of hexamethonium to patients with congestive failure exerts beneficial results.[10-13] It seemed, therefore, of interest to investigate the effect of hypotension induced by hexamethonium on renal hemodynamics and on the excretion of water and electrolytes in patients with edema of cardiac origin.

CLINICAL MATERIALS AND METHODS

Twenty patients were studied, including two normal subjects, seven hypertensive patients without congestive heart failure, five hypertensive patients with congestive heart failure, and six normotensive cardiac patients with congestive heart failure of various degrees. Further clinical details are given in Table I. All patients received a balanced hospital diet restricted in sodium. The studies

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were carried out in the morning after an overnight fast of about fourteen hours. The patients received water freely prior to and during the experiments and remained in the recumbent position throughout the studies.

TABLE I. CLINICAL DATA ON TWO CONTROL SUBJECTS, SEVEN HYPERTENSIVE PATIENTS WITHOUT FAILURE, AND ELEVEN PATIENTS WITH CONGESTIVE HEART FAILURE

NAME	SEX	AGE (YEARS)	CLINICAL DIAGNOSIS	AVERAGE BLOOD PRESSURE (MM. HG)
A. *Control Subjects*				
I.B.	f.	46	Duodenal ulcer	115/70
L.M.	f.	34	Rheumatoid arthritis	120/90
B. *Hypertensive Patients*				
Z.H.	m.	57	H.V.D.	180/110
B.H.	f.	45	H.V.D.	230/140
C.C.	f.	40	H.V.D.	205/115
M.R.	m.	54	H.V.D.	170/105
J.G.	f.	50	H.C.V.D.	230/145
S.G.	m.	42	Essential hypertension	150/100
M.F.	f.	45	Essential hypertension	160/100
C. *Patients With Congestive Heart Failure*				
A.G.	m.	55	R.H.D.	105/85
A.R.	m.	40	R.H.D.	110/90
Y.R.	m.	59	R.H.D., A.S.H.D., A.F.	130/95
R.M.	f.	20	R.H.D., A.F.	120/90
L.W.	f.	53	H.C.V.D.	225/160
M.A.	m.	42	R.H.D., A.F., cardiac cirrhosis	130/80
S.M.	f.	44	Cor pulmonale	130/85
A.B.	m.	36	R.H.D., toxic nodular goiter	120/80
Y.Y.	m.	22	R.H.D., A.F.	120/95
M.P.	f.	54	R.H.D., H.C.V.D., A.F.	160/95
E.B.	f.	55	R.H.D., A.S.H.D., A.F., diabetes	175/110

H.V.D. = Hypertensive vascular disease, H.C.V.D. = Hypertensive cardiovascular disease R.H.D. = Rheumatic heart disease, A.S.H.D. = Arteriosclerotic heart disease, A.F. = Auricular fibrillation.

Blood pressure readings were taken by the auscultatory method at short intervals throughout the experiments; venous pressure was measured both at the beginning and at the end of the studies.

Glomerular filtration rate was determined by the clearance of inulin, and renal plasma flow by the clearance of sodium para-aminohippurate, (PAH) using the constant infusion method. Inulin was determined by the method of Roe and associates,[14] sodium PAH by the method described by Smith and his associates.[15] Sodium, chloride, potassium, hematocrit, hemoglobin concentration, total plasma protein, albumin, and globulin were determined in the first and last blood samples. The percentage change in Plasma Volume at the end of

TABLE II. RENAL FUNCTION AND ELECTROLYTE EXCRETION AFTER ADMINISTRATION OF HEXAMETHONIUM (C_6)

PATIENT	C_6 (MG.)	PERIOD (MIN.)	B.P. (MM. HG)	VENOUS PRESSURE (CM. WATER)	URINE VOLUME (C.C. PER MIN.)	GFR*	RPF*	FF	$U_{Na}V$ (MEQ. PER MIN.)	$U_{Cl}V$ (MEQ. PER MIN.)	U_KV (MEQ. PER MIN.)	$PV_2/PV_1 \times 100$ (PER CENT) FROM Hct. AND Hgb.	$PV_2/PV_1 \times 100$ (PER CENT) FROM T.P.
A. *Control Subjects*													
I.B.		control	105/70	9	3.5	95	492	.193	.236	.295	.079		
	20	17	100/65		3.9	80	445	.179	.116	.229	.065		
	+	19	105/65		1.4	93	475	.196	.187	.246	.065		
	.4/min.	22	105/70	6	1.3	89	490	.181	.204	.270	.115	117	112
L.M.		control	115/75	7	10.3	133	624	.213	.122	.124	.045		
	10	15	90/65		3.0	134	540	.248	.146	.133	.026		
	+	15	120/90		1.2	132	577	.229	.198	.165	.027		
	.2/min.	17	120/85		2.0	158	628	.251	.311	.269	.055		
		14	130/95	8.5	2.4	157	572	.275	.307	.274	.072	102	103
B. *Hypertensive Patients Without Congestive Heart Failure*													
Z.H.		control	170/100	14	1.6	67	426	.157	.152	.183	.095		
	20	16	100/75		0.4	20	139	.147	.038	.055	.035		
	+	15	98/75		0.3	47	384	.122	——	.009	.044		
	.3/min.	13	95/70		0.4	58	503	.116	——	.009	.075		
		16	105/75	5.5	0.6	61	467	.131	——	.024	.111	108	103
B.H.		control	220/125	16	6.6	73	405	.181	.585	.494	.120		
	20	16	200/115		4.3	64	375	.172	.415	.350	.091		
	+	13	190/125		4.0	66	389	.170	.427	.345	.091		
	.35/min.	15	185/115		3.0	69	348	.198	.375	.269	.076		
		15	175/120		2.7	75	381	.196	.332	.258	.071		
		17	168/115		2.8	78	420	.187	.288	.225	.069		
		14	165/115	12.5	2.9	78	394	.197	.276	.241	.070	106	105
C.C.		control	220/130	7.5	3.4	81	457	.178	.129	.142	.056		
	20	15	190/125		0.6	42	228	.185	.043	.052	.020		
	+	17	195/135		0.8	88	487	.180	.099	.103	.039		
	.25/min.	15	195/135		0.5	70	392	.178	.106	.087	.037		
		16	190/135	5	0.7	80	462	.173	.111	.126	.042	114	110

M.R.		control	190/115	3.5	5.6	73	422	.173	.472	.351	.164		
	25	16	140/95		2.0	37	210	.174	.175	.150	.068		
	+	15	130/95		0.4	33	217	.153	.011	.022	.034		
	.25/min.	17	135/98		0.3	37	286	.130	.009	.009	.040		
		15	120/90	2.3	0.4	49	389	.125	.008	.008	.058	112	—
J.G.		control	240/145	13	8.2	100	346	.288	.713	1.032	.129		
	20	15	168/108		2.0	29	100	.297	.189	.250	.038		
	+	15	150/100		0.8	43	193	.222	.042	.081	.048		
	.1/min.	15	155/105		1.1	78	358	.219	.069	.108	.139		
		14	165/110		0.8	59	270	.221	.044	.072	.094		
		14	170/110	8	0.8	69	304	.226	.046	.085	.099	121	119
S.G.		control	143/108		1.5	115	480	.239	.104	.141	.101		
	25	13	110/85		1.0	82	297	.274	.047	.091	.084		
		13	100/80		0.8	108	469	.231	.029	.086	.106		
		12	100/80		0.7	100	392	.255	.020	.080	.103		
		15	110/100		0.9	107	445	.242	.032	.109	.130		
		15	115/100		0.9	104	410	.255	.042	.113	.119		
		16	120/100		0.9	105	412	.254	.059	.130	.125		
		15	125/105		1.0	104	412	.253	.075	.145	.092	127	125
M.F.		control	165/110		5.2	121	436	.257	.416	.376	.068		
	20	15	155/105		5.3	135	433	.310	.403	.330	.095		
		15	140/95		2.6	129	436	.296	.382	.341	.102		
		16	140/105		3.9	138	485	.285	.560	.486	.117		
		15	150/105		4.7	126	489	.258	.590	.474	.118		
		9	150/105		5.1	110	443	.249	.436	.402	.100	106	107
C. *Patients With Congestive Heart Failure*													
A.G.		control	120/70	4.5	4.7	74	244	.303	.049	.075	.066		
	25	16	95/60		3.9	67	218	.307	.045	.062	.035		
	+	16	85/60		1.9	54	208	.257	.060	.073	.033		
	.25/min.	17	85/60		0.8	57	213	.268	.052	.071	.037		
		11	90/60	5	0.7	57	183	.311	.041	.058	.051	120	120
A.R.		control	125/85	30.5	0.8	50	217	.230	.064	.073	.042		
	30	19	105/65		0.4	33	101	.319	.024	.036	.023		
	+	16	105/85		0.4	40	176	.229	.004	.017	.030		
	.3/min.	27	105/85	19.3	0.3	37	191	.192	.003	.009	.031	115	115

TABLE II.—CONT'D

PATIENT	C_6 (MG.)	PERIOD (MIN.)	B.P. (MM. HG)	VENOUS PRESSURE (CM. WATER)	URINE VOLUME (C.C. PER MIN.)	GFR*	RPF*	FF	$U_{Na}V$ (MEQ. PER MIN.)	$U_{Cl}V$ (MEQ. PER MIN.)	U_KV (MEQ. PER MIN.)	$PV_2/PV_1 \times 100$ (PER CENT) FROM Hct. AND Hgb.	$PV_2/PV_1 \times 100$ (PER CENT) FROM T.P.
C. *Patients With Congestive Heart Failure.—Cont'd*													
Y.R.		control	110/85	9	0.7	65	208	.311	.029	.023	.036		
		16	100/70		0.4	46	155	.294	.010	.013	.032		
	25	16	95/70		0.5	68	227	.298	.015	.016	.050		
	+	14	90/65		0.5	65	224	.289	.021	.019	.051		
	.3/min.	15	80/60	13.5	0.4	68	221	.306	.028	.022	.059	124	—
R.M.		control	135/80	9.5	10.3	97	385	.252	.145	.054	.075		
		16	100/68		6.9	72	342	.211	—	.010	.051		
	20	14	100/70		4.8	67	311	.214	—	—	.031		
	+	15	98/75		2.7	66	315	.209	—	.017	.028		
	.12/min.	16	105/78	13	7.5	78	407	.192	.048	.026	.021	115	—
L.W.		control	270/150	12.5	7.2	77	285	.269	.345	.302	.041		
		17	195/105		1.9	34	149	.230	.058	.089	.018		
	25	17	175/110		0.5	65	343	.188	.032	.029	.035		
	+	15	180/115		0.6	66	308	.214	.060	.041	.041		
	.2/min.	15	185/115		0.5	62	266	.234	.070	.053	.034		
		16	200/120	10	0.6	65	278	.235	.097	.077	.039	105	—
M.A.		control	140/80	31	0.8	31	163	.190	.009	.002	.021		
		16	100/60		0.5	13	66	.195	.008	.001	.012		
	20	19	100/70		0.3	17	99	.172	.006	.001	.012		
	+	15	98/60		0.3	17	116	.147	.010	—	.011		
	.16/min.	16	100/60	18.5	0.2	12	86	.143	.006	.001	.009	115	—
S.M.		control	150/85	14.9	8.4	78	499	.156	.026	.007	.100		
		18	125/70		4.2	60	366	.164	.018	—	.062		
	25	16	125/73		0.8	56	379	.148	.006	—	.067		
	+	16	120/68		0.9	78	505	.154	.006	.002	.085		
	.22/min.	9	118/65	13.7	0.9	77	505	.152	.005	.002	.081	104	—

A.B.		control	110/65	4	3.5	109	635	.172	.317	.308	.045		
	25	16	108/65		2.1	77	480	.160	.146	.169	.033		
	+	16	100/65		1.1	86	526	.163	.094	.103	.021		
	.28/min.	13	100/68		0.7	100	544	.183	.090	.079	.033		
		14	98/60	2.5	0.8	110	645	.171	.097	.087	.032	116	—
Y.Y.		control	125/100	4	0.7	78	221	.351	.062	.031	.047		
	25	15	120/95		2.7	82	238	.345	.034	.022	.061		
	+	15	120/90		4.1	78	228	.341	.047	.033	.047		
	.25/min.	16	120/90		3.2	70	213	.327	.057	.041	.038		
		16	115/90		1.8	66	204	.321	.086	.055	.033		
		13	110/90	2.5	1.6	65	203	.320		.060	.033	117	105
M.P.		control	160/100	4.5	3.8	72	302	.238	.063	.069	.049		
	25	16	130/90		1.2	41	180	.230	.024	.035	.025		
	+	14	100/70		0.7	86	393	.218	.006	.030	.048		
	.25/min.	15	110/70		0.8	71	367	.194	.015	.058	.070		
		15	110/75	4.5	0.7	61	341	.178	.021	.050	.074	106	102
E.B.		control	145/115	8.5	1.5	28	151	.187	.091	.110	.056		
	20	17	120/85		1.1	36	178	.199	.098	.111	.066		
	+	15	120/85		0.9	37	179	.208	.094	.108	.063		
	.15/min.	16	115/80		1.3	32	185	.173	.103	.118	.061		
		15	120/80	7	1.4	29	186	.154	.097	.116	.058	100	108

FF = filtration fraction, Hct. = hematocrit, Hgb. = hemoglobin, T.P. = total plasma protein.
*Milliliters per minute per 1.73 square meters.

each experiment (PV_2) as compared with the initial value (PV_1), expressed by the term $PV_2/PV_1 \times 100$, was calculated from the hemoglobin and hematocrit by the formula:

$$\frac{Hgb_1}{Hgb_2} \times \frac{1\text{-}Hct_2}{1\text{-}Hct_1} \times 100$$

and in most instances also from the values of total plasma protein by the formula:

$$\frac{TP_1}{TP_2} \times 100.$$

After three control periods, hexamethonium (C_6) bromide was added to the sustaining fluid containing inulin and PAH, and at the same time another quantity of the drug was also injected into the tubing near the vein. The amount of the drug varied from 0.12 to 0.4 mg. per minute for the slow infusion, and from 20 to 30 mg. for the single rapid injection. One of the normal control subjects received only 0.2 mg. per minute by slow infusion and 10 mg. by rapid injection. Two hypertensive patients received only the single rapid injection. The effects of the drug on renal hemodynamics and on excretion of water, sodium, potassium, and choloride were followed for four to six periods of about fifteen minutes each.

RESULTS

The pertinent data of eighty-seven observation periods after the administration of hexamethonium are given in Table II. Different types of reaction of renal function and water and electrolyte excretion to the drug are shown in Figs. 1 to 4.

Systemic Circulatory Adjustments.—The blood pressure fell in all patients, but not in the two normal control subjects. The drop in blood pressure in the hypertensive patients, including those with congestive failure, was significantly greater than in the normotensive cardiac patients. For all patients with hypertension the maximal decrease in mean blood pressure in any one observation period was between 16 and 63 mm. Hg (average 39 mm. Hg), whereas in the normotensive patients with failure the maximal falls ranged between 8 and 29 mm. Hg (average 20 mm. Hg).

The venous pressure decreased in most cases following the injection of hexamethonium, but small rises also occurred. However, as venous pressure readings were taken only at the start and the end of the experiments, changes that might have occurred during the experiments were not recorded. In two patients with severe failure (A. R. and M. A.) the venous pressure fell from the very high initial values of 30 and 31 cm. water to 19.3 and 18.3 cm., respectively.

Renal Hemodynamics.—The changes in GFR and in effective RPF observed in these studies were similar to those previously reported.[24] Fig. 1 shows an example of the most commonly found type of reaction of these functions, as well as of water and electrolyte excretion. GFR was lowered for some periods in most patients. One patient (E. B.), with very low initial values, showed small rises in GFR lasting throughout the experiment, and transient rises were found in some

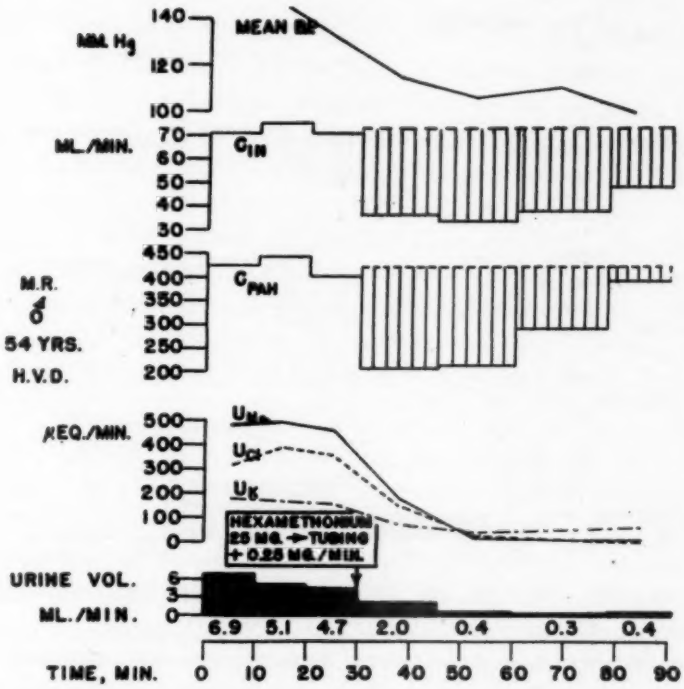

Fig. 1.—Depression in blood pressure, glomerular filtration rate (inulin clearance), renal plasma flow (PAH clearance), urine volume, and urinary electrolyte excretion after hexamethonium. Renal plasma flow is less depressed and returns more rapidly to control than the filtration rate.

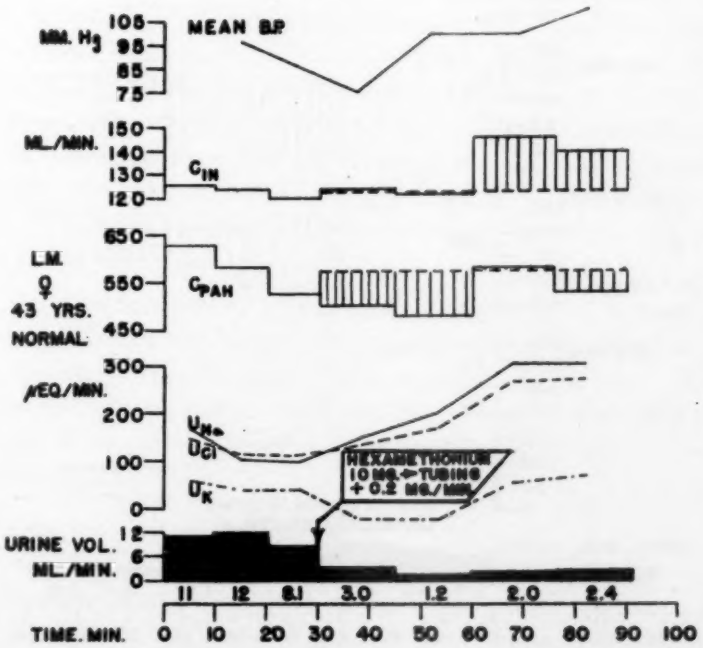

Fig. 2.—Rise in blood pressure, GFR, and urinary electrolyte excretion; urine volume is depressed throughout the experiment.

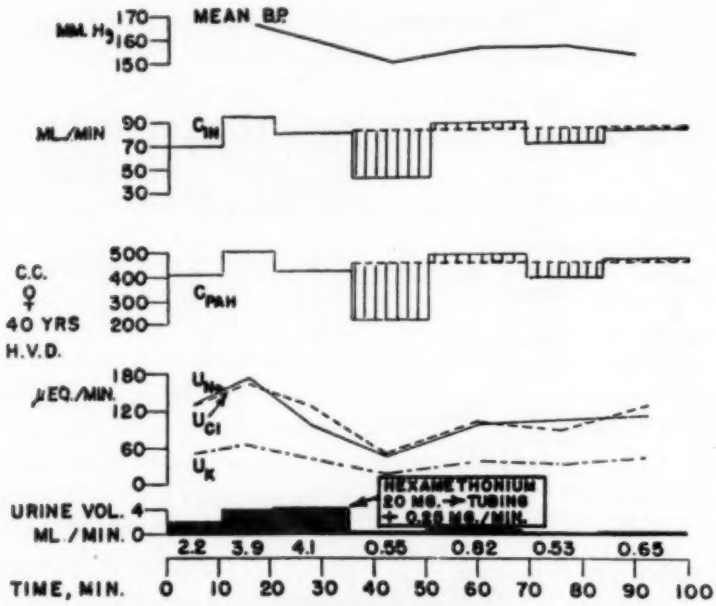

Fig. 3.—Renal functions and urinary electrolyte excretion are initially depressed, but return soon to control values. Urine volume remains depressed.

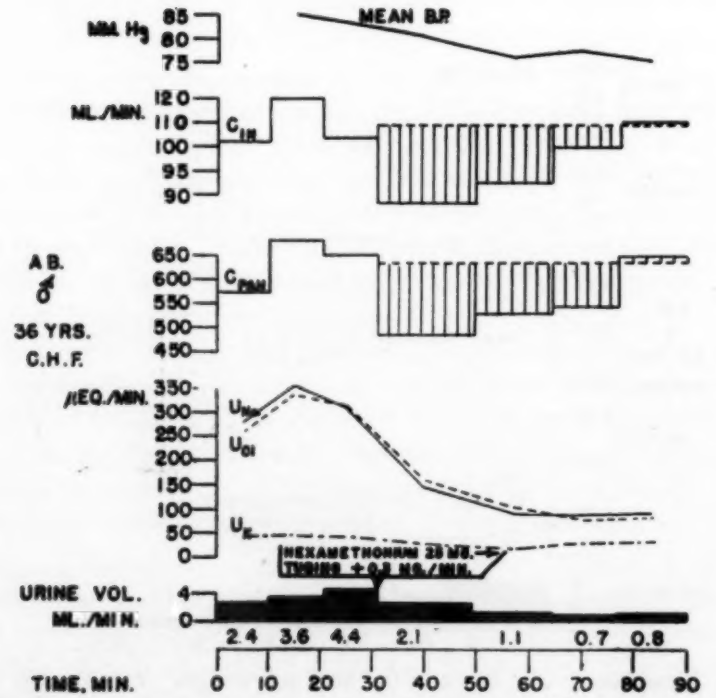

Fig. 4.—Slight depression of blood pressure, transitory depression of renal functions, marked and lasting depression of electrolyte excretion and of urine volume.

other patients. One of the normal subjects (L. M.) (Fig. 2) showed a rise of about 20 per cent in GFR toward the end of the experiment, together with an unexpected rise in blood pressure. In about half of the patients, GFR showed a definite tendency to return to preinjection levels, despite persistent reduction in blood pressure. Out of a total of 87 observation periods, GFR was lowered in 59 periods, raised in 11, and remained unchanged in 17 periods.

The changes in RPF tended to parallel those of GFR, but the falls in RPF were usually less marked than the falls in GFR (Fig. 1). There was a rise in RPF sustained for three or more periods in four patients (M.F., Y. R., M. P., and E. B.).

A comparison of the results in the two groups of patients, with or without congestive failure, did not reveal a significant difference in the behavior of renal hemodynamics.

Water and Electrolyte Excretion.—Urine flow decreased markedly in nearly all instances after the administration of hexamethonium. The decrease in urine flow usually paralleled decreases in either blood pressure or GFR, but occurred in many instances even if one or both of these latter functions increased or showed only minor changes [L. M. (Fig. 2), B. H. and C. C. (Fig. 3), M. F., S. M., and A. B. (Fig. 4)]. In one patient (Y. Y.) a rise in urine volume occurred during the first periods after the injection of hexamethonium, possibly related to an unusually low urine flow during the control periods.

Sodium and chloride excretion was markedly depressed in most instances after the administration of the drug. In four patients (A. G., M. A., Y. Y., and E. B.) in congestive heart failure who excreted very little sodium and chloride during the control periods, the drop in excretion of these electrolytes was very small, and in some periods even transitory rises occurred. In two subjects (L. M. and M. F.) moderate rises in GFR were accompanied by significant rises in sodium and chloride excretion (Fig. 2), in three other patients [B. H., S. M., and A. B. (Fig. 4)], in whom the GFR was initially reduced but returned later to preinjection levels, the excretion of sodium and chloride remained markedly low.

Potassium excretion after the administration of the drug was depressed in twelve, elevated in six, and essentially unchanged in two patients. In most instances the changes in potassium excretion were in direct proportion to the filtered load of this ion.

Changes in Composition of Blood and Plasma.—The hematocrit and the concentration of hemoglobin, total protein, albumin, and globulin progressively decreased in the majority of cases following hexamethonium. Therefore, the changes in plasma volume, calculated from the values for hemoglobin and hematocrit, and from total plasma protein, indicated in many instances considerable dilution of the plasma.

DISCUSSION

The reactions to hexamethonium of the patients in congestive heart failure in this study, both those with and without hypertension, are similar to those of the control group of hypertensive patients without failure. They agree closely with the results reported for hypertensive patients.[16]

The marked and prolonged reduction in urine flow observed in nearly all patients also agrees well with observations of other authors.[16-19] This phenomenon can be explained in most instances by reduction in GFR with delivery of a reduced amount of filtrate to the tubules, which continue to reabsorb at a normal steady rate.[8] However, in the instances of unchanged or even elevated GFR, observed at least temporarily in many instances, it must be concluded that the reduction in urine formation was caused either by hexamethonium directly, or by the general circulatory changes resulting from its administration. In one case (L. M., Fig. 2) the reduction in urine flow, in spite of a slight rise in blood pressure and in GFR, is especially striking and suggests the possibility of a specific antidiuretic action of hexamethonium on the renal tubules. This independence of a decrease in urinary volume from reduction in GFR and RPF has been stressed by Aas and Blegen[17] for TEAB and by Haugen and Blegen[18] and Moyer and Mills[16] for hexamethonium, and a possible specific antidiuretic effect has been discussed by the former authors.

The reduction in urinary volume was paralleled in most instances by a reduced excretion of sodium and chloride. As previously suggested for water, the slower rate of flow of the reduced amount of filtrate in the normally functioning tubules may also have promoted more complete absorption of salt. But here again, this mechanism alone cannot explain the changes observed in certain patients [B. H., S. M., and A. B. (Fig. 4)]. Although in these patients the GFR, during the second part of the experiment, returned to the original level, the excretion of sodium and chloride continued to decrease with corresponding changes in the load-to-excretion ratio. In patient B. H., for instance, the drop in load-to-excretion ratio for sodium reflects an increase in tubular reabsorption from an average of 93 per cent of the presented load to 97 per cent during the administration of hexamethonium.

It is of interest to note that, although in most instances the changes in water and salt excretion occurred in a parallel fashion, there were some instances in which the excretion of water diminished to a greater extent than the excretion of salt. In the above-mentioned case (L. M., Fig. 2) the reduction in urinary volume was even accompanied by a definite rise in the excretion of sodium and chloride. These observations suggest that under these experimental conditions the reabsorption of water and of salt was regulated by separate mechanisms. This fits in with the results of other experiments, in which the diuresis of water and the diuresis of salt was modified independently.[20]

The regulation of both water and salt excretions by factors other than changes in glomerular filtration has been postulated for a variety of experimental conditions, such as during salt loading or salt depletion,[21] after exercise,[22] upon changing from the sitting to the erect position,[23] during prolonged quiet standing,[24] in cases of orthostatic hypotension,[25] in arteriovenous fistula,[26] and also after hexamethonium.[16] In many of these experiments, specific alterations in tubular reabsorptive activity for sodium and chloride have been suggested, but in some of the experiments it is difficult to evaluate the influence of small changes in filtration rate on the magnitude of the load and the load-to-excretion ratio of

these electrolytes. However, if the reduction in water and salt excretion continues while the filtration rate returns to and above control values after an initial drop, as found by Moyer and Mills,[16] as well as in some of the above experiments, it must be concluded that the administration of hexamethonium initiated a chain of events which lead to actively increased tubular reabsorption of water and salt, unrelated to the changes in filtration.

As to the exact mechanism of this effect, no definite conclusions can be drawn from our experiments. It appears probable that the decrease in cardiac output, which can occur after the administration of hexamethonium[27,28] and the inadequate filling of the arterial tree, may serve as the stimulus for conservation or increase of the plasma volume by tubular retention of salt and water. The same purpose would also be served by a shift of fluid from the extracellular space into the vascular compartment. In fact, it appears from the observed changes in the hematocrit and the hemoglobin concentration that such a shift occurs during the hypotensive phase following the administration of hexamethonium. A decrease in hematocrit after hexamethonium may also be found in the tabulated data of Moyer and associates,[27] and similar observations have recently been reported for other hypotensive agents by Hueber.[29] These changes form an interesting contrast to the rise in hematocrit which has been observed after the administration of sympathicomimetic drugs such as epinephrine,[30] norepinephrine,[30,31] and aramine.[32] Conversely to what happens after administration of hypotensive drugs, the sympathicomimetic agents appear to cause a shift of fluid from the vascular compartment into the interstitual fluid space related to the rise in blood pressure.

From our observations and from corresponding reports in the literature it can be concluded that the administration of hexamethonium and of similarly acting drugs may favor, at least temporarily, the retention of salt and water, both by reduction in the filtration rate and also by increased active tubular reabsorption. These physiologic mechanisms may occasionally become important from a clinical point of view, if other factors abetting edema are present. Thus, as pointed out by Rønnov-Jessen,[9] it may be hazardous to use ganglionic blocking agents in hypertensive patients who are already close to decompensation. However, in the majority of cases, it is improbable that a transient reduction in filtration rate after hexamethonium and similar drugs will lead to salt and water retention. This follows from the common observation, which has also been experimentally confirmed,[33] that a normal salt and water balance can be maintained even with chronically reduced filtration rate.

As to the reported clinical improvement of congestive heart failure during treatment with hexamethonium, the data gained from short-term experiments can at best give only a hint as to the possible mechanism. Thus, it may be signficant that the venous pressure usually decreased after the administration of hexamethonium, most markedly so in the cases with pathologically high initial values (M. A., A. R.). This is consistent with the suggestion made by Kelley[11] and Burch[13] that the beneficial influence of hexamethonium in cases of congestive failure is due to an unloading effect on the venous part of the circulation.

On the basis of clinical reports and of experimental data, it appears that the effect of hexamethonium and similar drugs in cardiac patients depends on their clinical condition: patients with frank failure, and especially those with high venous pressure, may be expected to benefit from the drug; those with borderline failure and with a tendency to retain salt may occasionally be thrown into frank congestive failure by the renal mechanisms discussed above.

SUMMARY AND CONCLUSIONS

The rapid intravenous administration of hexamethonium to patients in congestive heart failure brought about changes in renal hemodynamics similar to those observed in hypertensive patients without failure. In both groups of patients, GFR and RPF were usually depressed, the former to a greater degree than the latter. Both GFR and RPF tended to return to control values, while the blood pressure was still reduced.

In both groups of patients the excretion of water and salt was nearly always markedly decreased during the hypotensive phase after administration of the drug. Although there was usually a close correlation between the changes in GFR and the excretion of water and salt, there were some instances of persistently depressed urinary volume and salt excretion even after return of GFR to control values. Occasionally, increases in GFR were paralleled by increased excretion of sodium and chloride, but, nevertheless, there was a reduction in water excretion.

The changes in renal hemodynamics alone are insufficient to explain the observed changes in water and salt excretion in all instances. Therefore, it is concluded that the administration of hexamethonium caused an increase in active tubular reabsorption probably by separate mechanisms for water and for salt.

The retention of fluid by the kidneys, together with a shift of fluid into the vascular compartment, brought about a dilution of the plasma with decrease in hematocrit and hemoglobin concentration.

Renal retention of fluid after hexamethonium may occasionally precipitate congestive failure. On the other hand, improvement in the clinical state of certain patients with congestive failure may be explained by the fall in venous pressure which follows the administration of the drug.

SUMMARIO IN INTERLINGUA

Le reduction de function renal e de excretion de aqua e electrolytos, previemente describite como occurrente in hypertensivos post administrationes intravenose de hexamethonium, esseva etiam observate in similemente tractate patientes con edema cardiac. Le reduction del excretion de sal e aqua esseva in parte independente del alterationes in le fluxo plasmatic e filtration glomerrular del renes e debe esser ascribite al augmentate reabsorption tubular e possibilemente a un specific effecto antidiuretic.

Le observate reduction del hematocrite e del concentration de hemoglobina es ascribite a un transferimento de fluido verso le compartimento vascular que es causate per le reducite rendemento cardiac e le diminuite plenation del arbore arterial.

Il es concipibile que le retention renal de fluido durante tractamentos a agentes de blocage ganglionic precipita a vices un disfallimento congestive. Del altere latere, melioration del stato clinic del patientes con franc disfallimento congestive es explicabile per un reduction del pression venose que es usualmente causate per le droga.

We wish to thank Mrs. Lisa Ullmann and Mr. Alexander Maerzon for valuable technical assistance.

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THE RELATION OF PECTUS EXCAVATUM TO HEART DISEASE

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PECTUS excavatum (funnel chest, trichterbrust) is a congenital thoracic deformity consisting of dorsal displacement of the sternum with costochondral concavity from side to side as well as the concavity from above downward. The depression is usually deepest a little above the xiphisternal junction. While the deformity is generally symmetrical, at times the costal cartilages on one side may be more sharply incurved than on the other.

Several mechanisms have been proposed for the production of this anomaly. Brodkin[1] feels that the anterior portion of the diaphragm, originally derived from the septum transversum, has had an arrest in development, resulting in a deficiency of the musculature of this portion. Brown[2] is of the opinion that a neuromuscular imbalance exists, whereby the anteroposterior fibers of the diaphragm are overstimulated. Lester[3] places the difficulty in a shortening of the anterior tendon of the diaphragm. Under any circumstance, breathing would tend to retract the lower sternum during inspiration, and, in fact, paradoxical respiratory movement of the sternum is regularly seen in patients with pectus excavatum, who are young enough to have flexible costal cartilages. Sweet[4] and Ravitch[5] point out that the deformity is observed at birth, almost with the first respirations of the infant, and the maximal concavity of the depression is generally well cephalad to the point of diaphragmatic attachment. The problem, then, may well be one of overgrowth of the ribs, as suggested by Flesch,[6] rather than diaphragmatic pull being the primary factor. McKusick[7] notes the occurrence of pectus excavatum with Marfan's syndrome (an association one of us, M.M.R., has seen several times) a condition in which he feels there is defective connective tissue. Scurvy and rickets on one hand, and obstructive lesions in the upper respiratory tract on the other hand probably play no role in this condition in most cases. A familial history is elicited in a significant number of cases.

All theories agree that the primary defect involves the anterior chest wall. Since the process is a dynamic one and is operative during the years of growth and development, secondary changes involving the vertebral column, the paravertebral musculature, and the thoracic viscera are prone to develop. Thus, during the first few years of life, children appear to be more pot-bellied than usual, with accentuation of the normal thoracic kyphosis and lumbar lordosis. As the deformity continues to progress, the older child or adult appears thin,

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round-shouldered, slightly stooped with head thrust forward, and of generally asthenic habitus. The volume of the thoracic cavity is necessarily decreased with variable degrees of compression and rotation of the lungs, heart, mediastinum, and great vessels.

The operation for pectus excavatum was put in proper perspective by the detailed review of Ochsner and De Bakey,[8] in 1939, and by the series of patients presented by Lincoln Brown[9] in the following year. Subsequent publications[4,10-16] have firmly established pectus excavatum as a congenital anomaly amenable to surgical correction.

The history of surgical therapy goes back to Sauerbruch's[17] operation, in 1913, upon an 18-year-old boy with dyspnea and intolerance for even mild exercise. With the slightest exertion he would develop violent palpitation and a feeling of pressure, so that he could not work. The pulse was irregular, and severe dyspnea and extreme irregularity of the heart beat followed slight exertion. Three years after Sauerbruch's operation (resection of the fifth to ninth left costal cartilages and the corresponding left side of the sternum) the pulse was perfectly regular and the patient could work twelve to fourteen hours a day without difficulty. For the next thirty-five years, surgeons experimented with one type of operation or another, with relief of symptomatic distress but unsatisfactory cosmetic results.

The extensive pertinent literature of the last fifteen years expresses increasing satisfaction of surgeons with the operation, with respect both to physiologic and cosmetic results. There seems not to be a corresponding awareness on the part of cardiologists and pediatricians as to the significance of the lesion and the satisfaction with which it can be dealt with surgically.

Bill[18] recently obtained twenty-five replies to a questionnaire submitted to American surgeons and physicians, one-third of whom stated that there would be no organic symptomatology resulting from severe pectus excavatum in adults. The literature is replete with statements of similar doubts, often despite obviously significant and attributable clinical and anamnestic findings.[19-23]

Much emphasis has been placed upon the differential attribution of symptoms to funnel chest on the one hand, and congenital or rheumatic heart disease on the other. This problem may often arise in the course of routine school or pre-employment physical examinations, or in mass chest x-ray surveys. More important than confusion with other conditions is the fact that profound physiologic disturbances may occur in funnel-chested individuals. Actually the important pathologic significance of pectus excavatum has long been well documented.

Sauerbruch's[24] second patient, eighteen years after his first, was a young girl with severe funnel chest and marked phenomena of cardiac displacement. In this patient he divided the costal cartilages on both sides and elevated the sternum by traction on a wire passed behind it. The result was ultimately good and all symptoms were relieved.

Hoffmeister[25] reported the case operated upon by Lexer. The patient was a 19-year-old boy with a congenital trichterbrust and a two-year history of precordial pain, exertional dyspnea, and palpitation. The heart was displaced to

the left. Operation (removal of the sternum and fifth to ninth costal cartilages on both sides) brought a great measure of relief. Lexer had planned to replace the sternum and is sometimes thought to have done so, but Hoffmeister stated that the thorax spread and the gap was too wide to retain the sternum. There remained slight exertional dyspnea, but the precordial pain and palpitation were gone and the heart returned to a normal position.

Alexander[26] (1931) reported two cases. The first patient was a 16-year-old boy alleged to have injured the sternum in wrestling four years before. The deformity appeared gradually in association with pain, dyspnea, and some dysphagia. Operation (division of five costal cartilages on each side, a T sternotomy, and skeletal traction on the sternum) relieved all his symptoms.

His second patient was a 20-year-old girl with a sternum depressed after an automobile accident. She had severe precordial pain, dyspnea, and palpitation, with some relief from operation.

Carr's[27] (1933) first patient, a 19-year-old girl, complained of faintness, dyspnea upon exertion, and rapid cardiac action. She was once diagnosed as having mitral disease and twice was discharged from a nurses' training school on account of her poor health. There was a slight systolic precordial murmur (a regular finding in these patients). The rhythm was regular. The heart was displaced to the left by a fairly marked funnel chest. Four months after operation (Lexer type operation with resection of sternum and cartilages) the murmur was audible in only a very small area, cardiac consciousness was gone, and she could walk a mile or more a day. Carr's second patient, a 13-year-old boy with a deep funnel chest, cyanosis, and moderate dyspnea, was not operated upon.

Edeiken and Wolferth[19] (1932) studied ten patients with funnel chest. One 33-year-old man had an uncomplicated case with history of paroxysmal atrial fibrillation of eight years' duration. The electrocardiograms were thought not to show definite abnormalities attributed to the funnel chest. In most cases the heart was displaced, usually to the left and upward.

Ochsner and De Bakey[8] (1939), in their exhaustive review, reported a 21-year-old woman with a severe deformity, who had a sensation of tightness and constriction in the chest, a constant, dull, aching precordial pain, and increasingly severe dyspnea. They performed bilateral costochondral resections and a transverse sternal osteotomy. A year later she had an excellent cosmetic result, was relieved of all symptoms, and had gained 7 pounds in weight. In the discussion of the paper of Ochsner and De Bakey, Sandison reported a 13-year-old girl with a severe pectus excavatum, cyanosis, and dyspnea so severe she was confined to bed. The patient was described as "well and active" after operation.

Brown's[9] (1939) second patient was a 22-year-old man whose exertional dyspnea was relieved by operation. Reporting seven successful operations, Brown took pectus excavatum out of the group of rare deformities infrequently treated, and established a rational and successful operative procedure which is the basis of most present-day techniques. He resected 2 cm. segments of cartilages 4, 5, 6, and 7 and sectioned cartilage 3, excised the xiphoid process, divided the attachments of rectus and diaphragm to the sternum, performed a transverse wedge osteotomy at the angle of Louis, wired the fifth costal cartilage to the sternum, and used wires for traction on the sternum.

Nissen's[28] (1944) patient, a 20-year-old chemist, complained of shortness of breath, precordial pressure, and easy fatigability. The heart was displaced to the left and rotated so that the right ventricle was in contact with the left chest wall. In a two-stage operation the sternum was removed, cartilages were resected, and the sternum was turned to lie transversely and with its original ventral surface facing dorsally. No progress reports were given.

Sweet[4] (1944) reported two sisters; the 14-year-old girl had attacks of palpitation and tachycardia lasting four to twenty-four hours and associated with pain and cyanosis. The heart was displaced far to the left and enlarged. Sweet's operation, in which the cartilages are wired to the sternum after resection of small chondral segments and a transverse osteotomy of the sternum, improved the appearance of the chest but failed to prevent further paroxysms of tachycardia. The 5-year-old sister of Sweet's first patient had a funnel chest without symptoms.

Lester[10] (1946) reported eight cases of funnel chest. One patient, a 6-year-old girl, had severe exertional dyspnea and was a patient in the cardiac clinic "for systolic and diastolic murmurs and cardiac incompetence." She was unable to play with other children or to run 50 feet. Eighteen months after operation she was completely relieved. A number of other patients also had definite cardiac symptoms. In older children Lester resected the involved cartilages, separated the xiphoid process, performed a cuneiform osteotomy of the sternum, and used wires for traction on the distal sternal segment.

Teplick and Drake[20] (1946) studied nine adult patients. All had some degree of dyspnea or chest pain attributable to the deformity, none serious. In eight of the nine the roentgenograms showed well-marked cardiac displacement to the left.

Evans[21] (1936) studied sixteen "healthy" subjects with depressed sternum, ranging in age from 15 to 36 years. The apex beat was displaced outward and a systolic murmur was present in every case. In nine of the cases there was moderate scoliosis.

Sutton's[22] (1947) patient was a 30-year-old woman with severe funnel chest and scoliosis who had increasing dyspnea and palpitation of a few months' duration. She had obvious severe heart failure and dyspnea. The heart beat was regular at the rate of 140 beats per minute and there was a soft systolic apical murmur. The patient died and autopsy revealed only a dilated heart.

Master and Stone[23] (1949) studied twenty-five patients with funnel or flat chest referred for consultation because of the presumptive diagnosis of heart disease. In sixteen patients the heart was displaced to the left, in ten the pulmonary artery appeared abnormally prominent, and in 60 per cent a loud systolic murmur was heard. There were varying electrocardiographic changes. Eight patients had precordial pain, ten had dyspnea, six had palpitation, and there was a scattering of other symptoms, such as tachycardia and fatigue.

In a later (1950) report of forty-two cases, Lester[29] says that cardiac symptoms produce a decrease in exercise tolerance in nearly all cases, and that moderate or incapacitating cardiac disability may occur.

In the discussion of Lester's paper, Brown related his experience with twenty-seven cases and stated that he had had uniformly poor end results in symptomatic cases, obtaining only slight improvement in respiratory function, although the cosmetic results were good.

Wahren's[30] (1950) patient, a 10-year-old girl, had shown dyspnea and weight loss for a year. The electrocardiogram was normal. Nine months after operation (resection of costal cartilages and xiphoid process, elevation of sternum upon a transversely placed tibial graft) she had gained weight and was free of symptoms.

Dorner and associates[31] (1950) reported a 28-year-old man with a severe pectus excavatum and marked cardiac symptoms. For eighteen months he had had palpitations coming on in attacks associated with weakness, dizziness, precordial pain, dyspnea, and sweating. These disabling attacks were induced by slight exercise and relieved by rest. Pulse rate in these attacks was 200 beats per minute. Electrocardiographic studies showed a supraventricular tachycardia with a block varying from 5:1 to 1:1, tall, peaked P waves. Angiocardiographic examination showed dilatation of the right atrium and ventricle. In the discussion of this case Miscall reported a child with pectus excavatum and severe dyspnea with cardiac displacement. Operation gave complete relief. On this occasion, Brown was more enthusiastic about symptomatic improvement after operation, having abandoned all fixation of the sternum, except across the transverse cuneiform osteotomy.

Gordon Murray[31a] mentioned five patients with funnel chest referred to him because of cardiac symptoms and all relieved by operation. The two patients reported in detail were cardiac invalids. Both returned to full activity after an extensive procedure involving a full-length midline sternotomy and multiple divisions of each rib or cartilage from the second to the costal margin on each side, both pleurae being opened widely. Fixation was maintained by buried wire sutures and by traction wires.

One of us (M.M.R.),[5] in 1951, reported the case of a 28-year-old man with a severe pectus excavatum and a history of two attacks of cardiac failure in eight months. Electrocardiographic studies showed atrial fibrillation and marked delay in precordial transition, indicating cardiac rotation. Cardiac displacement and rotation were shown in the angiocardiogram. Cardiac catheterization showed a cardiac output one-half as great as the expected normal and elevations in the right atrial and ventricular pressures. Circulation time was delayed. Respiratory function studies showed figures at the lower end of the normal range. At operation five costal cartilages were resected on either side and a transverse osteotomy of the sternum performed, permitting it to be elevated into the corrected position.

A year later the electrocardiogram was normal but for a slight delay in precordial transition, the circulation time was normal, cardiac catheterization showed a doubling of the cardiac output to a normal figure and significant fall in the right atrial and ventricular pressures, and respiratory functions were entirely normal. The patient is asymptomatic and performs heavy work now, six years after operation, reporting that his physical endurance allows him to work his small farm as well as to drive a municipal bus.

Another adult man showed, on cardiac catheterization, a systolic plateau on the upswing of the right ventricular pressure such as is often seen in constrictive pericarditis.

The operation which we employ consists in subperichondral resection of all deformed costal cartilages from their junction with the sternum to the lateral limit of the deformity. From four to six cartilages are usually involved on each side. The xiphisternal junction is divided, and the intercostal bundles divided from the sternum. The sternum is left as a peninsula attached only at its cephalad extremity. In older patients a one-half centimeter segment near the sternum of the first normal cartilage above the deformity is also removed. A transverse cuneiform osteotomy of the sternum is performed at the level of the intercostal space above the highest cartilage resected. The sternum is elevated into the corrected position which is maintained by sutures in the bone and periosteum across the osteotomy. In the older patients in whom a sliver of an additional cartilage has been removed, the cut ends are fixed with sutures, providing additional support. The intercostal bundles are tacked lightly back to the sternum. No external traction, fixation, or supports are required. A midline incision is used. Paradoxical respiration has not proved to be a problem, and oxygen is not regularly needed. The so-called "limited operation" of Lincoln Brown, dividing the xiphoid and one or two cartilages on either side, is never employed. A recent patient who had had this operation was said by his parents to have a deformity as bad as before that operation, or worse. The result of the definitive operation was entirely satisfactory.

Our experience now covers fifty patients operated upon; forty-three children, the youngest three months of age, and seven adults, the oldest 38 years of age. There has been one death, the second patient operated upon, of immediate and overwhelming wound infection. There have been no other significant complications. The results in terms of thoracic reconstruction, improvement in general well-being, appetite, weight gain, and exercise tolerance have been uniformly satisfactory.

The present report concerns, particularly, thirteen patients studied since 1952, of whom eleven were operated upon. These individuals were referred because of the cosmetic appearance of the chest, suspicious murmurs, or cardiac symptomatology. Our findings are correlated with those described in the literature and concepts presented which may help to clarify some of these observations and explain the mechanism for the production of disability in these patients.

SYMPTOMATOLOGY

In the younger patients, the history as given by the mother was noted. Regular regurgitation of a small amount of food, fifteen to twenty minutes after meals, was reported and observed in patient L. A. Gastrointestinal symptoms unassociated with heart failure are thought to be uncommon in this condition. However, as pointed out previously,[15,32] improved eating habits and weight gain have been observed in infants and older children after corrective surgery. It is not inconceivable that extrinsic pressure on the esophagus may occur.

Four patients had complaints of dyspnea on exertion. In addition, the two oldest patients (aged 16 and 27) noted a definite decrease in exercise tolerance, so much so that they could no longer engage in athletics as they previously had. Palpitations were encountered in one patient. There were no complaints of chest pain, cough, paroxysmal dyspnea, or peripheral edema.

It is of interest that two male patients had overheard comments by their playmates concerning their deformity and related this voluntarily to the physician. They wanted reassurance concerning the eventual cosmetic result upon the chest.

PHYSICAL EXAMINATION

Of the thirteen cases constituting the present study group, eleven had severe or moderately severe degrees of funnel chest deformity, and in two the deformity was not severe. The depressions of the anterior chest wall generally began at the second or third intercostal space and extended to the ensiform cartilage (Fig. 1). In several cases, the deformity was rather broad, extending almost to the midclavicular lines on either side. In no instance was there any complicating rheumatic or congenital heart disease. The four patients, 15 years of age and older, were thin, tall, and gracile. Blood pressures and pulses were within normal limits, with the exception of patient M.Z., who had a persistent tachycardia of about 100, even during sleep.

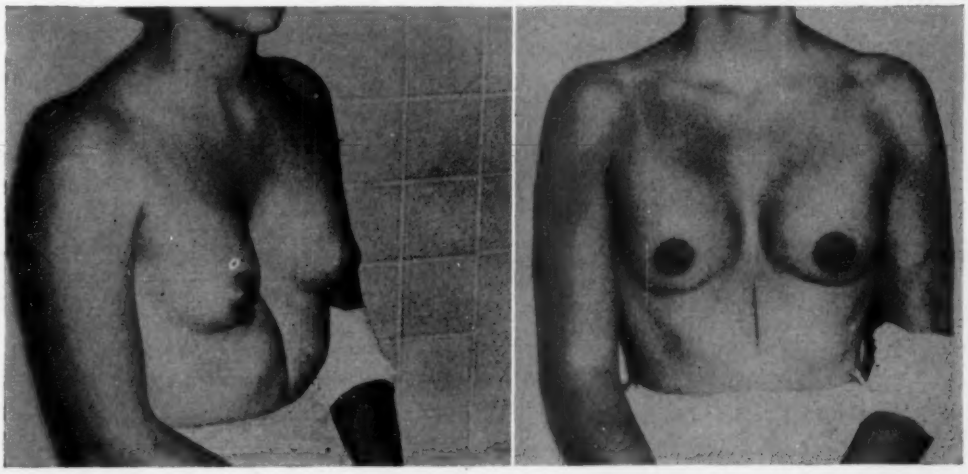


Fig. 1.—Patient M. Z., 28-year-old secretary, before operation. The funnel chest deformity is marked and seen to extend from the level of the second intercostal space to epigastrium, but limited to the median aspect.

Seven patients had systolic murmurs ranging in intensity from grades one to three. These were best heard along the left sternal border. In three instances, the systolic murmur disappeared postoperatively. The point of maximal impulse was palpable in the anterior axillary line in three patients. There were no evidences of congestive heart failure or lung disease in any case.

RADIOGRAPHIC EXAMINATION

The most conspicuous finding in the radiographs of the chest in the posterior-anterior position was the increased extension of the cardiac silhouette to the left. There was, however, no uniformity of the associated features. Some of the cases showed not only considerable extension to the left, but also to the right (Fig. 2), well beyond the shadow of the vertebral column. In others (Fig. 3), the right cardiac border could not be identified, since it appeared to fall within

the projection of the vertebral column. In the latter group, projection of the cardiac apex off the diaphragm was often seen associated with an increased prominence of a long segment of the main pulmonary artery. Since these features may be seen in normal individuals when the subject is rotated into a right

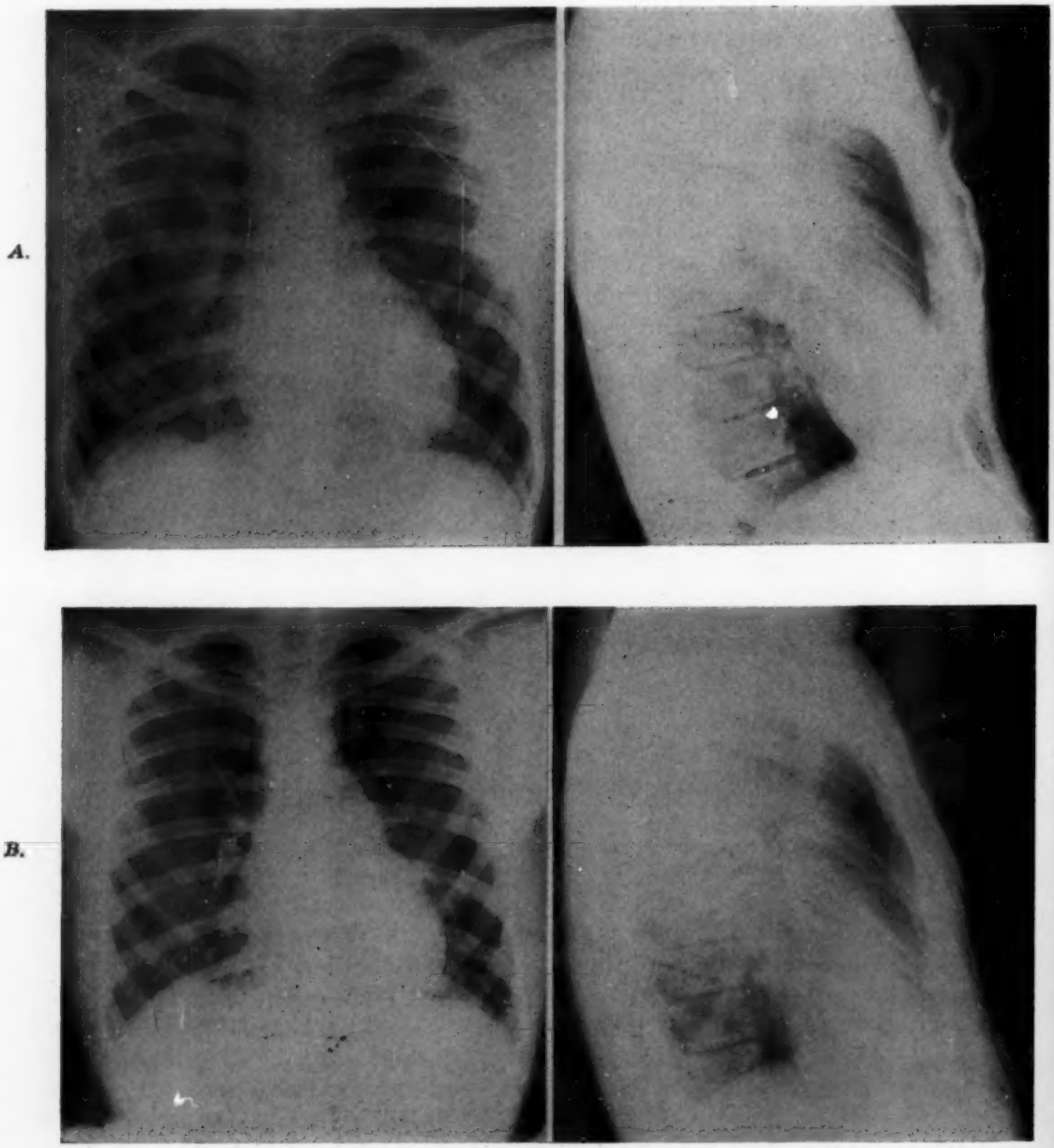
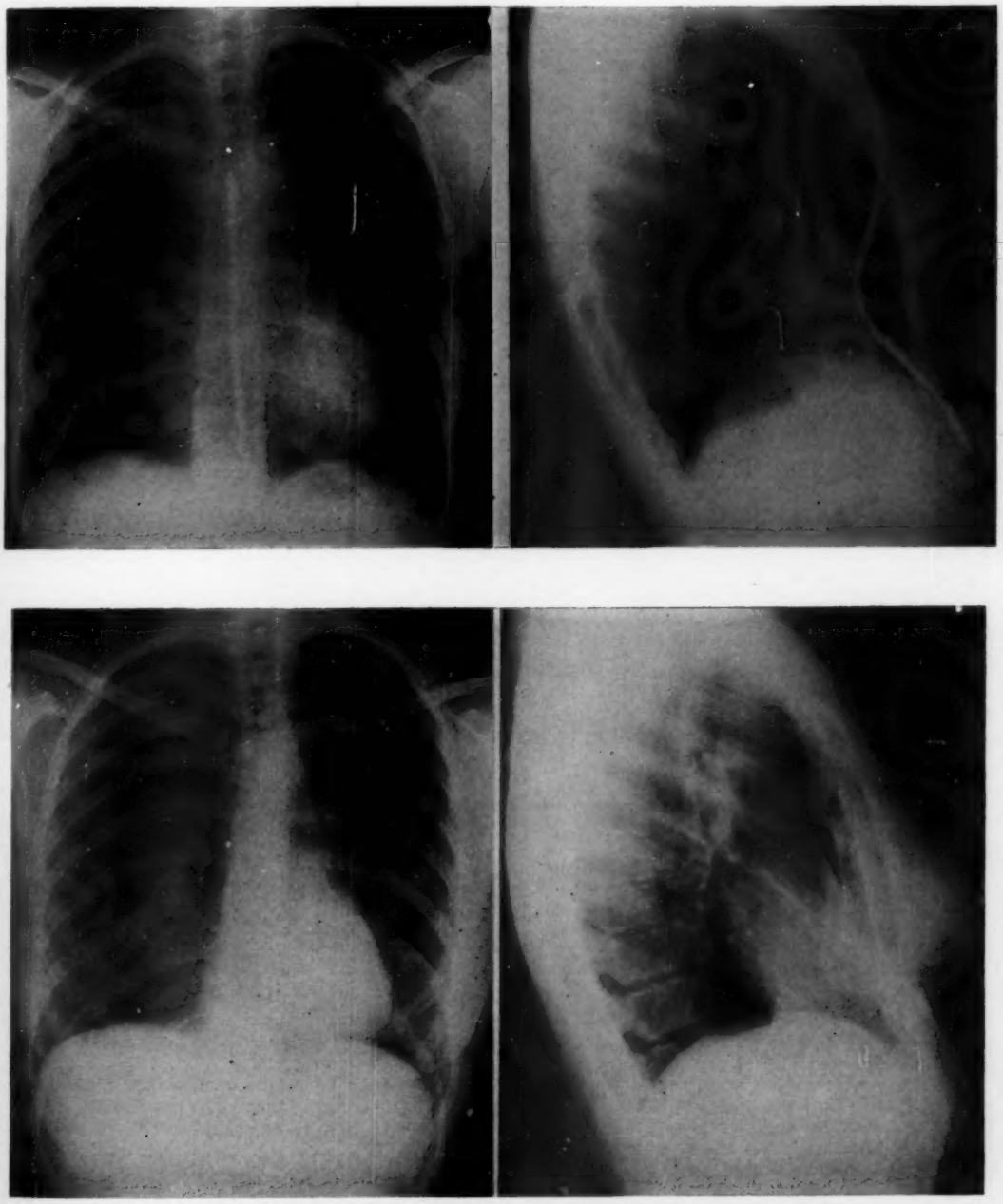


Fig. 2.—Patient F. B., 16-year-old boy. *A*, **Preoperative radiographic examination of chest. The patient's funnel chest deformity was deep and particularly broad, extending almost to the midclavicular lines on each side. The posterior-anterior projection reveals a broadened cardiac silhouette. The lateral view demonstrates the extent of the chest deformity through a roll filled with barium paste attached to the patient's skin with adhesive tape. Note the small posterior-anterior diameter of heart and chest ("Pancake Heart").**

B, **After operation. The diameter of the heart in the posterior-anterior projection is diminished, and the diameter of the heart and chest in lateral view is increased. Note the disappearance of the chest wall deformity as demonstrated by the barium paste.**

anterior oblique projection of a mild degree (5 to 10 degrees), it would appear that cardiac rotation played a significant role in the formation of the cardiac silhouette in the posterior-anterior view. Since the funnel chest deformity was severe in these cases, one can assume that with the excessive encroachment by



A.

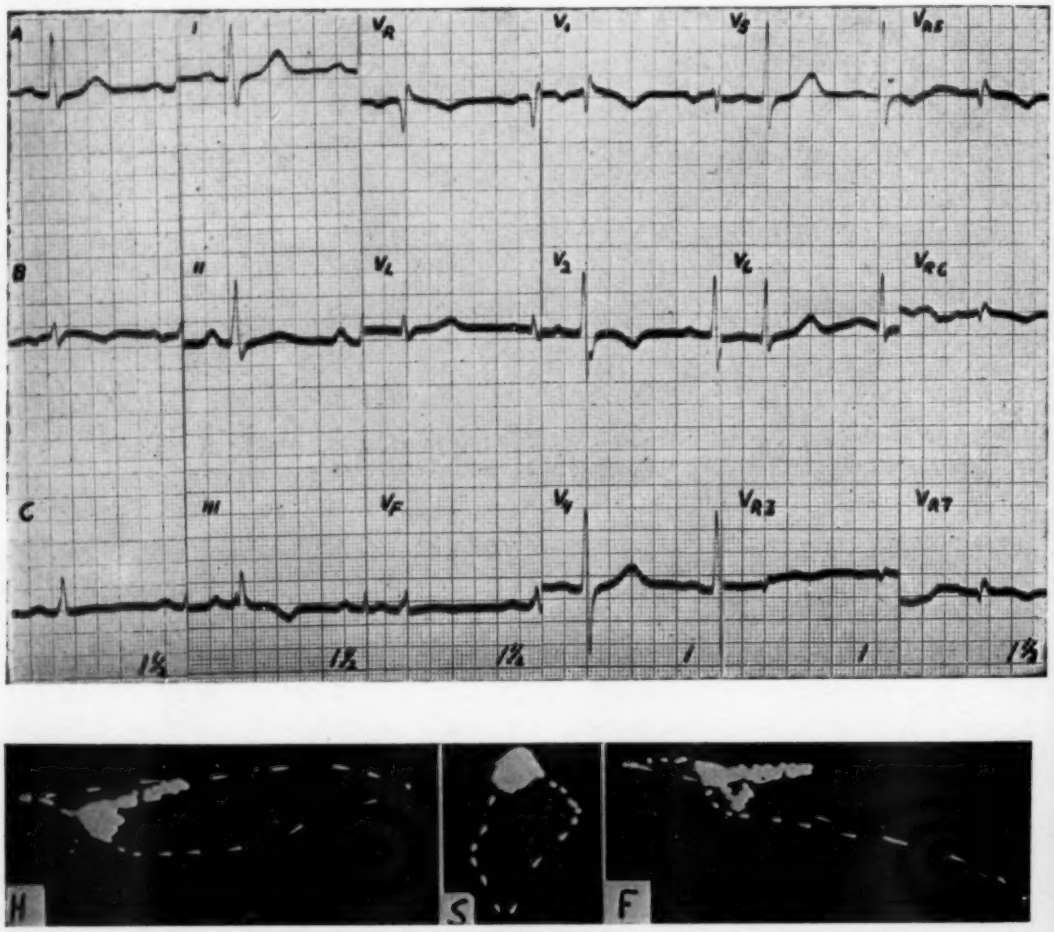
B.

Fig. 3.—Patient M. B., 28-year-old woman. *A*, **Preoperative radiographic examination. The posterior-anterior projection shows the heart displaced into the left chest and slightly rotated in a clockwise fashion. The lateral projection reveals the marked funnel chest deformity (barium paste). Its lateral limitation causes displacement of the heart rather than compression along the posterior-anterior diameter.**

B, **Postoperative radiographic examination reveals now a normal cardiac silhouette and position. The lateral view demonstrates a considerable improvement of the funnel chest deformity.**

the sternum upon the retrosternal space, the heart was displaced into the left hemithorax. This displacement causes a mild rotation in a clockwise fashion, because of the fixation of the cardiac pedicle. Other cases, particularly those not giving the appearance of cardiac rotation, have marked diminution of the posterior-anterior diameter of the heart in the lateral projection, giving the impression of a flattened structure.

Posterior displacement of the heart was not observed in any of our cases.



A.

B.

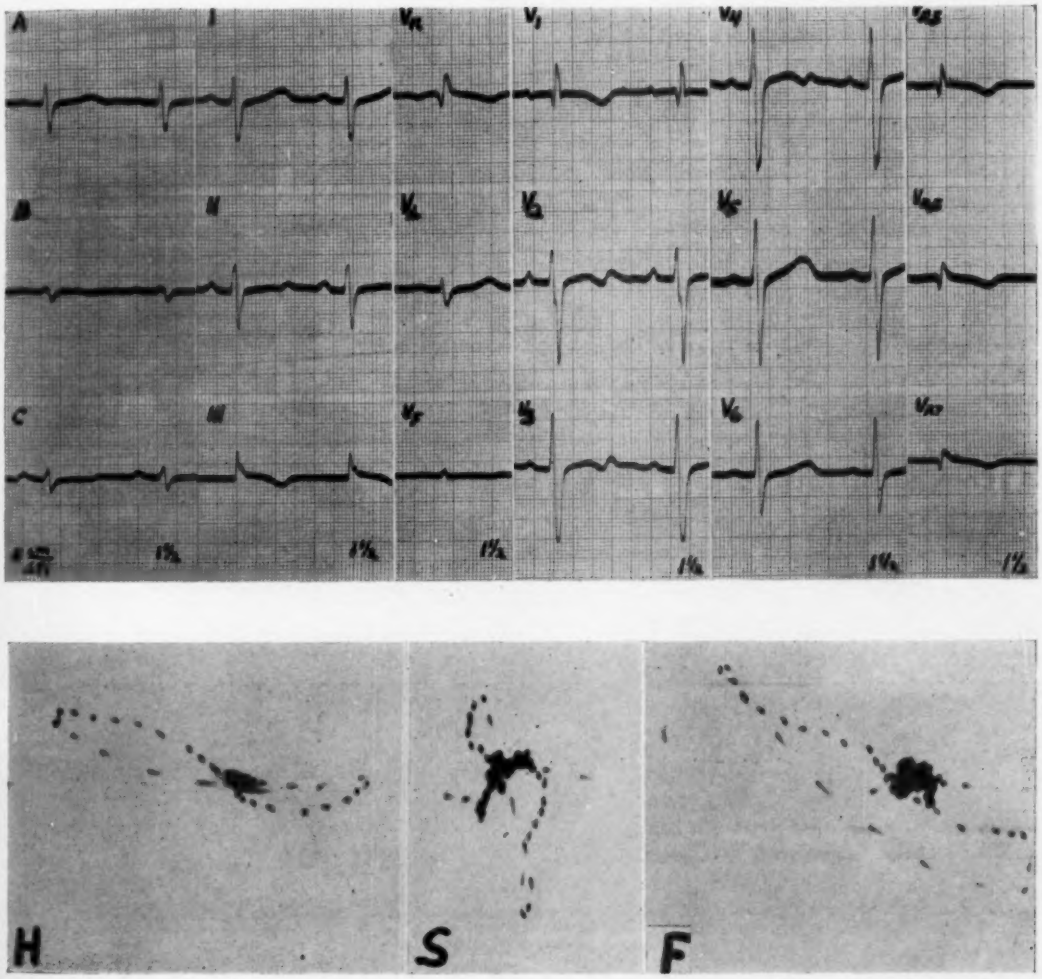
Fig. 4.—Patient S. S., 3-year-old boy. *A*, Preoperative electrocardiogram (recorded at 5 cm. per second) shows a regular sinus rhythm. An rSR′ is recorded over V_1 and right-sided chest leads with inverted T waves in V_1 and V_2.

***B*, The preoperative vectorcardiogram recorded with the cube technique of electrode placement shows a counterclockwise rotation in the horizontal plane with its terminal part right posteriorly. The timing as judged by the distance of the time-markers is normal. The right posterior "Pip" accounts for the rSR′ in right-sided chest leads. (*H:* horizontal plane; *S:* sagittal plane; *F:* frontal plane).**

THE ELECTROCARDIOGRAM AND THE VECTORCARDIOGRAM

All cases had sinus rhythm without extrasystoles. There was a tendency to right axis deviation in three and definite right axis deviation in two. P waves were notched only minimally in three individuals. The QRS duration was normal in every instance. The most unusual change observed was in the con-

figuration of the QRS complex in V_R and V_1. In eight of nine tracings, an rSr′ or rSR′ was observed (Fig. 4,*A* and 5,*A*). Botelho,[33] in five of thirteen cases, and Schaub,[34] in six of 108 cases of pectus excavatum, noted this pattern previously and referred to it as an atypical right bundle branch block of the Wilson type. We do not feel that this is the case in our patients because the vectorcardiograms are merely variations of the normal without indications of right bundle branch block. Representative examples are shown in Figs. 4,*B* and 5,*B*.



A.

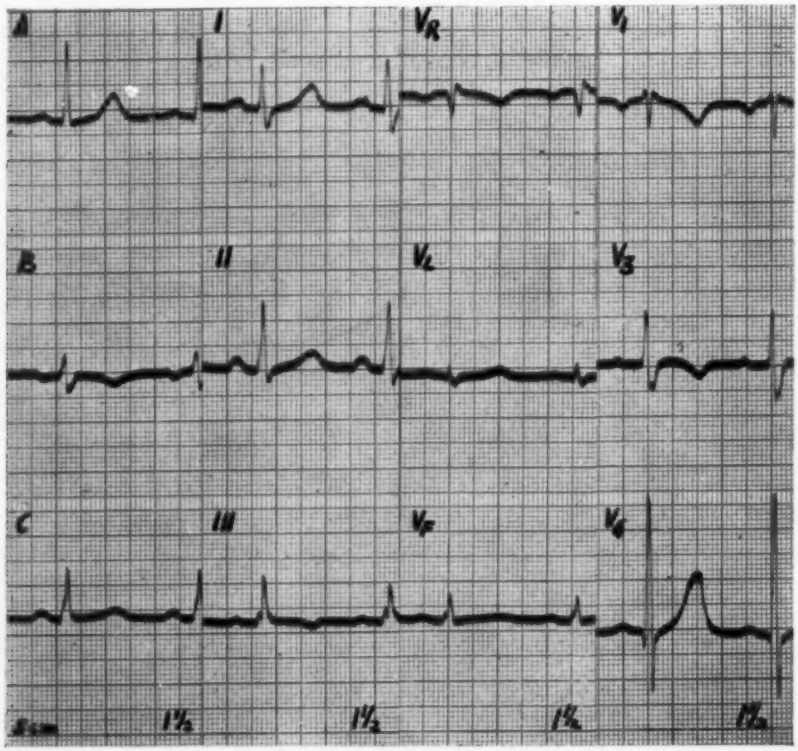
B.

Fig. 5.—Patient C. M., 8½-year-old boy. *A*, **Preoperative electrocardiogram shows regular sinus rhythm, right axis deviation, and a high and long R wave in** V_R. **The precordial leads show an rsR′ in** V_1 **and right-sided chest leads with inverted T waves. Diphasic T waves are seen up to** V_4.

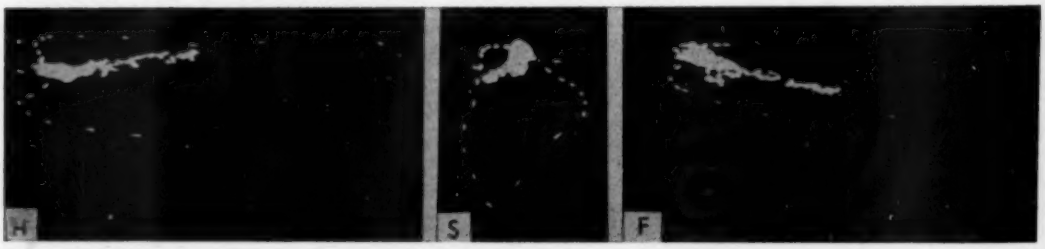
B, **The preoperative vectorcardiogram shows in the horizontal plane (*H*) an initial counterclockwise inscription to the left with a terminal right posterior segment. The latter projects to right-sided chest leads as an *R′*.**

Note the small right posterior and superior terminal appendage, which is best seen in the horizontal and sagittal projections. The reflection of this appendage accounts for the R′ registered in V_R and V_1. In the Wilson type block, this appendage is directed predominantly anteriorly and has a delay in its inscription. This was not seen in our cases. Furthermore, if one were to rotate this vectorcardiogram about 15 degrees in a clockwise direction, it would be indistinguish-

able from a vector normal in all respects. This actually occurred significantly postoperatively in Case R.W. and to a lesser degree in some of the others (Figs. 6,*A*, *B*; 7,*A*,*B*).



A.

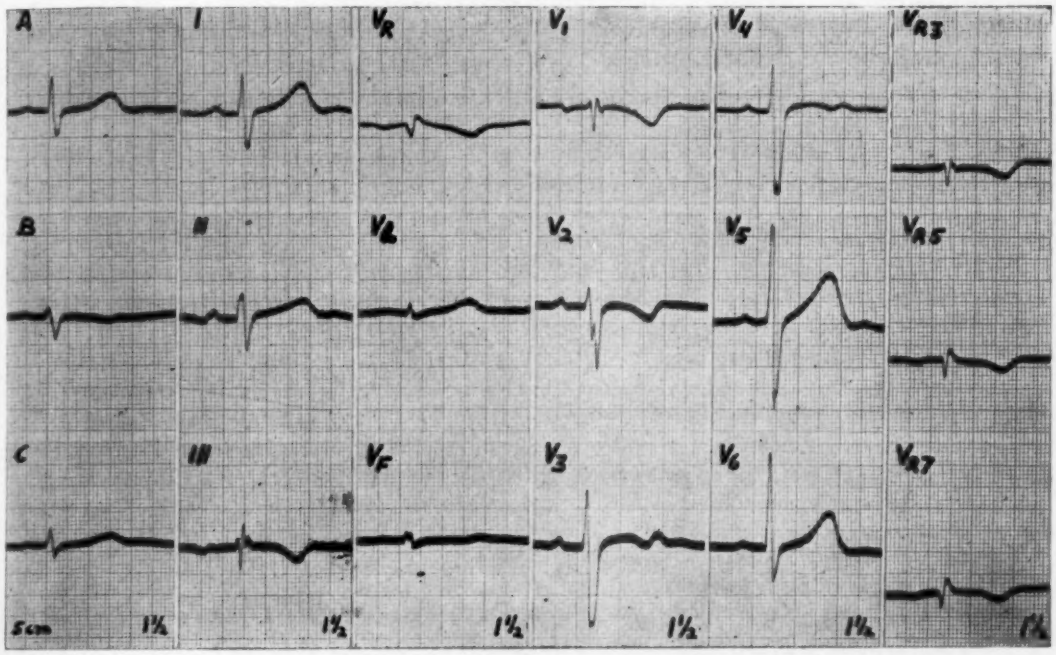


B.

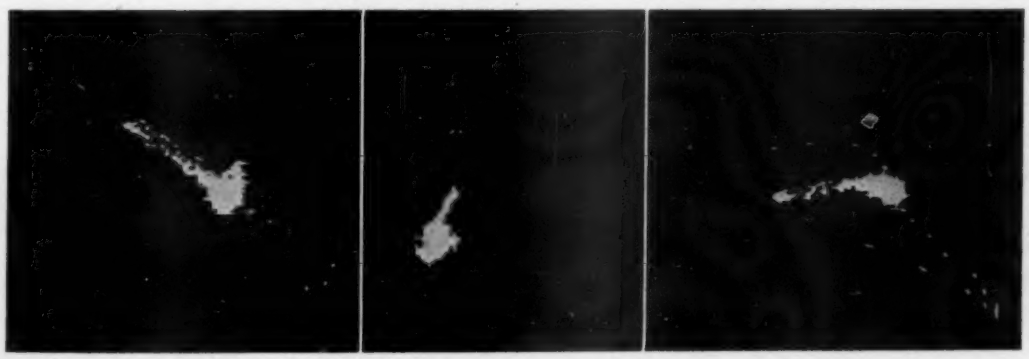
Fig. 6.—Same patient as Fig. 4. ***A*, The postoperative electrocardiogram shows diminution of the R′ wave in V_R and V_1.** ***B*, The postoperative vectorcardiogram reveals, no longer, the right posterior terminal segment in the horizontal plane projection seen previously (Fig. 4,*B*).**

It is important to realize that the anatomic configuration of the chest wall makes the application of the chest electrodes difficult. For that reason, T-wave changes in the precordial leads may be difficult to evaluate. In our cases, the T waves became upright, commencing with V_4 and remained so to V_6. The T-wave inversions observed by Dressler and Roesler[35] can also be explained by rotation of the cardiac vector. The anatomic rotation of the heart may cause a similar displacement of the vectorcardiogram, which then may be found more posteriorly oriented than usual. Thus, the T loop will project as an upright T

wave in chest leads further to the left than found in most normal individuals. The T loop in the vectorcardiogram is essentially concordant as seen in Figs. 4, 5, 6, and 7,*B*. No findings indicative of myocardial damage were observed.



A.



B.

Fig. 7.—Same patient as Fig. 5. ***A,*** **The postoperative electrocardiogram shows only a small R′ in V_R and V_1. The comparison to the preoperative record (Fig. 5,*A*) is in this respect particularly striking.** ***B,*** **Postoperative vectorcardiogram—the terminal segment is less to the right and more posterior (horizonal plane projection *H*).**

PHYSIOLOGIC STUDIES

Preoperative cardiac catheterization was performed in two of the adult patients.* Their case histories follow.

F. B., a 16-year-old high school student, was admitted to the Mount Sinai Hospital on Feb. 17, 1954, with the chief complaint of exertional dyspnea. For several years he had noted the gradual inability to continue sustained activity in vigorous sports, such as basketball and hockey. It

*Cardiac catheterizations were performed by the catheterization group of The Mount Sinai Hospital under the supervision of Dr. A. J. Gordon.

was necessary for him to stop after five minutes because of dyspnea and fatigue. The past history was negative except that he was known to have a chest deformity since birth.

Physical examination revealed a thin, but well-developed youth in no distress. The blood pressure was 125/65 mm. Hg and the pulse rate 82. There was a marked funnel chest deformity which was rather broad, as well as deep. The point of maximal cardiac impulse was not displaced. There was a Grade 2 systolic murmur best heard in the pulmonary area with an accentuated and reduplicated P_2. The remainder of the examination was within normal limits.

One year following operation, this youth reports that he plays an entire game of basketball without interruption.

M. Z., a 28-year-old secretary, was admitted to the Mount Sinai Hospital on Oct. 19, 1953, with complaints of pounding of the heart and exertional dyspnea. These symptoms began several years before admission. Concomitantly she noted a decrease in exercise tolerance. She could no longer play a full game of badminton nor could she swim more than one length of a pool, whereas previously several lengths were easily accomplished. The slightest exertion resulted in a forceful pounding of the heart. Her referring physician always found the pulse rate to be above 100. The past history was negative except that she was aware of a funnel chest deformity since early childhood. She had been treated for hyperthyroidism for some time, without benefit.

Physical examination revealed the patient to be a well-developed woman in no distress. The blood pressure was 115/80 mm. Hg and the pulse rate 104. There were no unusual findings in the head and neck. There was a very deep midline funnel chest deformity extending from just below the angle of Louis to the epigastrium (Fig. 1). The depression did not extend very far from side to side. The point of maximal cardiac impulse was outside the left midclavicular line. The heart sounds were of good quality and a Grade 1 systolic murmur was heard within the apex. The remainder of the examination was within normal limits. Eighteen months after operation, the patient reports that she has almost unlimited exercise tolerance.

In each instance, cardiac output determinations were made before and after ten minutes of standard exercise on a stationary bicycle. Patient F.B. revealed normal intracardiac pressures and oxygen saturations. His response to exercise demonstrated an excellent rise in cardiac output. Data of M.Z. revealed normal oxygen saturations and intracavitary pressures at rest. After ten minutes of exercise, there was a slight rise in pulmonary artery pressure. The cardiac output at rest was normal, but failed to rise, and actually fell slightly, with exercise. This response is, of course, distinctly abnormal.

There have been several reports of abnormal cardiac catheterizations in funnel-chested individuals. Lindskog's[36] Case C revealed a right atrial mean pressure of 22, with a cardiac output of 3.42 liters. After digitalization, the right atrial mean pressure was 6.5 and the cardiac output rose to 5.3 liters. One of Ravitch's[5] patients had high end-diastolic pressures in the right ventricle, when he had been thought to be out of congestive heart failure. In another patient, there was an intracardiac pressure tracing which was strongly suggestive of that seen in constrictive pericarditis. Maier,[5] in discussion of Ravitch's paper, discussed the catheterization results in one of his own patients in whom there was a marked increase in right atrial pressure after exercise.

The marked restrictions of the intrathoracic space in the cardiac region in these patients may not permit an increase of cardiac volume during exercise. This would restrict the cardiac chambers from receiving an increased venous return. This mechanism simulates to a certain extent the dynamics of constrictive pericarditis.

Ventilatory studies on M.Z. revealed a normal vital capacity. However, the maximal breathing capacity was 66 per cent of the predicted values. There was no evidence of impairment of alveolar gas exchange. These data were interpreted as indicative of some impairment of the bellows action of the chest. This result is in keeping with the more extensive studies of Brown,[2] who found that the maximal breathing capacity was diminished 50 per cent or more in nine of eleven patients with funnel chest, whom he studied.

DISCUSSION

Our experience would indicate that moderate to severe funnel chest, although compatible with normal activity and longevity, cannot be considered a benign musculoskeletal deformity. This is a condition wherein marked anatomic alterations of the thorax and secondarily of its viscera may result in profound disturbances of cardiorespiratory physiology.

In the past, it was felt by some that symptoms arising in affected individuals were a "direct outcome of the physical inactivity or mental anxiety resulting from unwarranted invalidism,"[18] or are "functional and similar to those observed in neurocirculatory asthenia or autonomic imbalance."[20] We cannot agree with these concepts, but feel as others do that when symptoms are manifest, they are a direct result of altered function of the cardiorespiratory systems. The several reports dealing with individuals in congestive heart failure whose symptoms have been relieved by surgical correction of the thoracic deformity are proof of this.

The radiographic findings are regarded to be of a twofold nature: (a) displacement of the heart into the left hemithorax with mild clockwise rotations, and (b) pancake appearance of the heart with an increase of the frontal silhouette to the left and right.

The cardiographic findings result from cardiac rotation and do not reveal any evidence of intraventricular conduction defect or myocardial involvement. Mechanisms for the production of circulatory embarrassment in affected individuals are probably the result of (1) cardiac rotation, with twisting and kinking of the great veins, thereby impeding the return of blood to the right heart; (2) distinct cardiac impingement, especially of the atria, resulting in cardiac arrhythmias, particularly of supraventricular origin (atrial flutter and fibrillation) and involvement of A-V conduction; (3) restriction of expansion of the heart, with resultant inability of the heart to deliver more blood on demand; and (4) decrease of respiratory reserve because the intercostal component of respiration is impaired.

For these reasons, and in view of the fact that the deformity is congenital, and unpredictably progressive, we feel that operation should be undertaken

1. In infants with marked deformity,
2. In infants with observed progression of the deformity,
3. In children and young adults with marked deformity, and
4. In adults who are symptomatic.

SUMMARY

1. Pectus excavatum is a congenital thoracic deformity which, in moderate and severe cases, may result in profound disturbances of cardiorespiratory physiology.

2. The radiographs of the chest in this condition indicate cardiac displacement, impingement, and rotation.

3. The electrocardiographic and vectorcardiographic findings are the result of cardiac rotation and do not reveal any evidence of intraventricular conduction defect or myocardial damage. The rSr′ or rSR′ pattern observed in V_1 is a variation of normal and does not indicate incomplete right bundle branch block.

4. Cardiac catheterization in one of the symptomatic adults was of great interest in that a normal cardiac output was observed at rest. After ten minutes of standard exercise, a definite fall in cardiac output was recorded, with only a minimal rise in pulmonary artery pressure.

5. The mechanisms responsible for cardiac disability in this condition are thought to result from

a. a decreased return of blood to the right heart,
b. cardiac arrhythmias secondary to atrial impingement,
c. restriction of expansion of the heart, and
d. a decrease in respiratory reserve.

6. This deformity can be corrected satisfactorily by operation with good physiologic and cosmetic results.

SUMMARIO IN INTERLINGUA

Post un revista del litteratura medical e chirurgic, le autores discute le relation inter pectore excavate e morbo cardiac super le base de un serie de 13 moderate o sever casos studiate depost 1952 per le autores mesme. Il existe un sufficiente corpore de datos pro supportar le assertion que pectore excavate pote seriemente afficer le functiones cardio-respiratori per (1) le limitation del plenamento cardiac e consequentemente del rendimento cardiac, specialmente post exercitio, (2) le production de arrhythmias cardiac per impingimento atrial, e (3) le reduction del reserva respiratori.

Le constatationes radiographic in iste condition es debite in certe casos al displaciamento del corde verso le sinistre hemithorace in combination con rotation. In altere casos le restringite diametro postero-anterior del thorace preveni le disveloppamento del corde in iste direction con le resultato de un corde de forma allargate e applattate. Le constatationes electro- e vectocardiographic es debite a rotation cardiac. Le resultatos obtenibile per interventiones chirurgic, specialmente in patientes de etate juvenil, es multo satisfacente.

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FIBROELASTOSIS IN ADULTS

A Review of the Literature and Report of a Case

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FIBROELASTOSIS (fetal endocarditis, endocardial fibrosis, congenital idiopathic hypertrophy of the heart, and congenital fibroelastosis) is a recognized pathologic entity in infants.[1-3] Few cases have been reported of a similar lesion in adults.[4-11] The etiology and pathogenesis of this cardiac lesion is unknown.[3,9,12] Rosahn[2] recently suggested that the disease is associated with generalized vascular changes, and that it is genetically determined. There is some difference of opinion as to what should be included as fibroelastosis in the adult. And, too, there is a difference of opinion referable to whether the lesion in the infant has the same etiology as that in the adult.[11,12]

The classical lesion generally accepted as fibroelastosis is nicely described in the paper by Gowing[12] from which the following is a quotation: "The heart is usually much enlarged and increased in weight. The myocardium, especially the wall of the left ventricle, is thickened and hypertrophied. There is dilatation of the chambers, the left ventricle being particularly affected, and the apex is rounded, so that the heart often assumes a globular shape. . . . On opening the heart striking changes are found in the mural endocardium. The left side of the heart, especially the left ventricle, is involved more often and more severely than the right side. The mural endocardium is thickened and opaque and gray or white in color. This change is usually diffuse, the thickened layer lining the whole chamber and covering the papillary muscles and trabeculae corneae. Sometimes the thickening is most pronounced just below the aortic valve. It may be diffuse in the left ventricle and patchy in the other chambers, or diffuse throughout the whole heart. . . . Deformities of the mitral or aortic valve are present in about 50 per cent of cases, while involvement of the pulmonary or tricuspid valve is less frequent. The valve leaflets are thickened and opaque and their edges are often 'rolled.' Fusion of the cusps may occur and the chordae tendineae may be thickened. Stenosis may result. . . . Between the endothelium and the myocardium is a thick layer composed of collagenous and elastic fibers, mainly disposed parallel to the surface; inflammatory cells are absent. . . . Fibrous-tissue bands from the endocardium may penetrate into the myocardium for a short distance and link up with other strands of connective tissue surrounding degenerate muscle fibers."

Cases considered to be fibroelastosis have been reported throughout the world. Williams and associates,[13] in 1954, gave a geographic summary of these

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cases. Except for the large number reported from Africa[13,14] a majority of the cases of fibroelastosis in both the infant and the adult have been reported from America.[12] Williams and associates[13] considered the cases of endomyocardial fibrosis in Uganda "to differ in no way" from the cases of fibroelastosis reported from America. Thomas and associates[11] think that endomyocardial fibrosis and endocardial fibroelastosis represent two distinctly different entities. Additional studies will be necessary to establish whether the African cardiac lesion (endomyocardial fibrosis) is the same or entirely different from the lesion (fibroelastosis) observed in America and in England. The lesion, as reported from Africa,[13,14] occurs much more frequently than the one in America.

A total of twenty-four cases of what may be considered as fibroelastosis in adults (16 years of age and over) now has been reported from America and England. A brief summary of the clinical and pathologic findings in this group of cases is given in Table I. Dammin and associates,[10] in 1951, reported that during the preceding four years they had seen fourteen clinical cases of fibroelastosis. Nine of these were studied at post mortem. Eleven of the fourteen cases were men. Most of them were between the ages of 40 and 60 years. No details of the individual cases were given, so they cannot be included in the above summary. In this collection of twenty-four cases (Table I) there were five women and nineteen men. Dennis and associates[1] in a study of a group of infants and children found the sex distribution to be 75 boys and 66 girls. The age of our cases varied between 17 and 71 years, with ten being 40 to 49 years of age. The heart usually was enlarged; only four of twenty-three cases weighed less than 400 grams. Thirteen weighed 500 grams or more. The systolic pressure usually varied between 100 and 140 mm. Hg, the lowest was 90 and the highest was 145 mm. Hg. The maximum diastolic pressure was 100 mm. Hg in one case, and 75 mm. Hg or less in five cases. The diastolic pressure usually varied between 80 and 90 mm. Hg. A systolic murmur was the most common type noted; however, in eight cases there were no murmurs observed. In three of the twenty-four cases there is no record of any auscultatory examination. An electrocardiogram was made in twenty-two of the twenty-four cases. Nine of these showed a bundle branch block. The voltage of the QRS complexes was low in six of the cases. T waves were inverted in eight. Either the right or left axis was deviated in eight cases. In none of the twenty-two cases where an electrocardiographic study was made was it normal. Gray[9] commented upon the fact that the ECG usually was abnormal; most often it showed low voltage and either a flat or inverted T wave in one or more leads. Dennis and associates[1] found abnormal electrocardiographic tracings in every instance of fibroelastosis in a group of thirty-seven infants and children. The most common deviation noted in these infants and children was a depression of the T waves; an inversion of the T waves was observed in only one lead in one patient. Gray[9] expressed the opinion that the blood pressure was low. However, in a review of these twenty-four cases we are not impressed by this feature.

The presenting clinical manifestation was myocardial failure almost routinely in these cases of fibroelastosis. The length of illness and the severity of symptoms varied widely. Mural thrombi on the left side of the heart with subsequent

TABLE I

CASE NO.	AGE	SEX	HEART WEIGHT (GRAMS)	B.P.	MURMURS	ELECTROCARDIOGRAPHIC EXAMINATION
1*	16	M	500	100/90	Gallop rhythm—loud blowing systolic murmur at apex	Sinus tachycardia—low voltage of the QRS complexes—inverted T waves in Lead I and flat T wave in Leads II and III
2	21	M	600	112/80	Soft systolic murmur at apex	Complete atrioventricular block and flat T wave
3	21	M	750	100/70	Faint, apical diastolic murmur	Ventricular tachycardia at a rate of 230. Right bundle branch block
4	42	M	425	135/100	No murmurs	Slurring and low voltage of the QRS complexes in the standard leads, low T waves in Lead I, slightly inverted T waves in Leads II and III, and upright T waves in Lead C F_4
5	43	M	700	120/95	No murmurs	Normal rhythm and pattern of hypertrophy of left ventricle. Subsequently sinus tachycardia and left bundle branch block
6	44	M	340	110/80	Moderately loud systolic murmurs, maximum at the lower end of sternum and at apex	Frequent premature ventricular beats and no discernible atrial activity. Low voltage of the QRS complexes, sagging S-T segments in Leads II and III, slightly elevated S-T segments in Lead C F_4 and low or flat T waves in all leads
7	46	M	450	100/65	No murmur	Left bundle branch block. Irregular rhythm at a rate of 70, a P-R interval that varied from 0.1 to 0.34 second and left bundle branch block
8	49	F	380	100/90	A soft apical systolic murmur and a short apical diastolic rumble	
9	50	F	490	114/80	No murmurs	Sinus tachycardia, with an atrial rate of 105 and bigeminy from premature ventricular beats. Slight right axis deviation, low voltage, and low or slightly inverted T waves
10	59	M	700	120/80	Gallop rhythm, no murmurs	Normal sinus rhythm, with occasional premature ventricular beats and right axis deviation. The QRS voltage was low, and there were nonspecific T waves changes
11	63	M	520	145/85	Slight systolic murmur at apex	Occasional runs of bigeminy and right bundle branch block
12	71	M	510	130/90	Many extrasystoles	
13	41	M	385	—	—	Repeated tracings showed either a right or left bundle branch block or complete heart block
14	47	F	420	90/95	—	Tracings showed evidence of myocarditis and suggestive of coronary infarction
15	28	M	350	120/80	Grade III apical systolic murmur. Pulmonic sound accentuated	Right axis deviation—a ventrical position of the heart as seen in the unipolar limb leads. The precordial leads showed a right ventricular pattern from V_1 to V_6, inclusive. The width of QRS was 0.07 second and the intrinsic deflection occurred early in all precordial leads

TABLE I.—CONT'D

CASE NO.	AGE	SEX	HEART WEIGHT (GRAMS)	B.P.	MURMURS	ELECTROCARDIOGRAPHIC EXAMINATION
16	40	M	650	126/80	Soft systolic murmurs at apex	Marked right axis deviation. Auricular fibrillation present with occasional ventricular premature contractions
17	35	M	500	100/70	The first sound was accentuated and a short, high pitched systolic murmur was heard	Right axis deviation—normal sinus rhythm present with sinus tachycardia and occasional premature contractions. The T waves were of low amplitude in all leads, and the T wave in Lead I was abnormal in form. The P wave in Lead II was of increased amplitude
18	35	F	460	106/88	No murmurs	Left axis deviation. The rhythm indicated a normal sinus mechanism. Conduction time of the QRS complex in Lead II measured 0.12 second. The T waves and the R-T segments had the form seen in the left intraventricular heart block of the concordant type. The P waves were matched in all leads
19	40	M	—	115/95	Soft systolic murmur and a protodiastolic gallop were heard at the apex	Right axis deviation, slight depressed S-T segments in Leads II and III, and low T wave
20	36	M	600	110/80	No murmurs	Normal rhythm with right axis deviation and normal conduction, low voltage complexes in all leads, flat T_1 and T_2, inverted T_3, and slight depression of S-T in Lead II.
21	18	M	750	130/80	No murmurs—later developed systolic murmur at apex	Incomplete bundle branch block with QRS of 0.13 second. P-R interval was 0.14 second. T_1 inverted and T_2 and T_3 were upright. Subsequently, A-V nodal rhythm, with bundle branch block. T_1 became diphasic, T_2 and T_3 inverted although no digitalis was given
22	29	M	470	110/80	No murmurs	Auricular tachycardia with complete bundle branch block and numerous ventricular premature beats. QRS measured 0.17 second, R was notched and T was inverted in all leads
23	31	M	640	110/60	Soft systolic murmurs at apex	Sinus tachycardia—left preponderance. The P-R interval was 0.15 second. The T wave was inverted in Lead I and II and upright in Lead III
24	47	F	560	114/86	—	Low voltage of the QRS complexes and low or slightly inverted T waves in all three leads

*Cases 1 to 12 reported by Thomas and associates[11]; 13 and 14 by Comeau[5]; 15 by Fienberg and Holzman[7]; 16 to 18 by Smith and Furth[6]; 19 and 20 by Gray[9]; 21 to 23 by Levy and Rousselot[4]; and 24 by McKusick and Cochran.[8]

embolication occurred in a high percentage of cases, and sometimes this was the immediate cause of death. An ante-mortem diagnosis of fibroelastosis apparently was never made; however, in one case (Case 7), it was suggested.[11] A correct clinical diagnosis apparently can be made sometimes in infants.[1]

Every effort should be made to study adequately all cases of fibroelastosis in an attempt to establish the etiology. With more cases the problem may be answered as to whether this is a disease entity with different pathologic manifestations occurring within the heart, as suggested by the African and American cases. The mechanism of the cardiac hypertrophy in fibroelastosis is fascinating. One usually considers that it follows dilatation. If fibroelastosis results in a constrictive mechanism in the endocardium, as has been suggested,[8] the question may be asked—When and how do dilatation and hypertrophy occur? A potential mechanism for cardiac hypertrophy as mentioned by Sodeman[15] may explain this. "Hypertrophy is certainly caused in many instances, perhaps in all, by stretching of fibers—by increase of their length at the beginning of systole. The long fiber produces more energy each time it contracts, and therefore, in time, hypertrophies. Yet the stretched fiber may produce more energy, not simply because it is lengthened, but because its tension is increased; animal experiments have yielded contradictory evidence on this point. If tension, rather than length, at the beginning of (or early in) systole is crucial, then the tense fiber produces more energy and hypertrophies whether it is long or not."

CASE REPORT

K. G., a white man, 38 years of age, developed a generalized skin eruption in September, 1953, which was diagnosed "leukemia cutis" by biopsy. The eruption subsided following irradiation; however, it did recur. In January, 1955, the patient was admitted to the M. D. Anderson Hospital with the same type of skin eruption as he had had two years previously. A biopsy at this time showed a lymphomatous infiltration of the dermis which was considered to be a "malignant lymphoma." There was a similar lymphomatous infiltration of the bone marrow which was considered to be leukemia. During hospitalization he was treated with irradiation, Purinethol and cortisone. An anemia, severe leukopenia, and thrombocytopenia developed four months preceding the time of death, which was May 10, 1955.

The patient was obese (290 pounds). At the time of hospitalization a routine chest film showed a heart that was considered to be within the upper limits of normal size. The blood pressure was 156 mm. Hg systolic and 100 mm. diastolic. There were neither clinical nor physical signs or symptoms to indicate a myocardial lesion. Four months later a roentgenogram showed the heart to be greatly enlarged. An electrocardiogram was normal. The blood pressure was 126 mm. Hg systolic and 80 mm. diastolic. Severe dyspnea, tachycardia, and edema of the feet and lower extremities developed several days before death.

The post-mortem examination was performed twelve hours after death. A few petechiae were present in the skin of the lower extremities. A small amount of straw-colored fluid was present in the serous cavities; 20 c.c. was present in each pleural space and approximately 50 c.c. in the abdominal cavity. There was no excess of fluid in the pericardial cavity. None of the lymph nodes were significantly enlarged. A few atypical cells were present in the sinusoids. The spleen weighed 850 grams. Many mononuclear and bizarre-shaped multinucleated cells were present in the pulp. Similar cells were located around the portal spaces in the liver, in the peripancreatic tissues, and diffusely infiltrated the kidneys, testes, endocardium, pericardium, myocardium, lungs, and bone marrow. This lymphomatous infiltration was considered to be a leukemic process.

The heart weighed 720 grams. The aorta appeared to be slightly smaller than normal. It measured 6.5 cm. in circumference at a point 3.5 cm. distal to the aortic valve. A minimal amount of arteriosclerosis was present in the aorta and coronary arteries. No areas of occlusion were found in the latter vessels. No significant pathologic changes were observed in the histologic study of the aorta and coronary arteries, although a variety of special stains were studied. An area of fibrosis 2 by 3.5 cm. was present in the epicardium over the right ventricle (Soldier's spot). This showed only collagen when studied by special techniques. All the cavities of the

heart were dilated. The wall of the left ventricle measured 18 mm. in thickness and the right, 6 mm. The aortic valve measured 7.5 cm. in diameter, the mitral 12.5 cm., the tricuspid 15 cm., and the pulmonary 8 cm. The entire endocardium of the left ventricle was smooth and pearl-gray in color (Fig. 1). A portion of the endocardium in the right ventricle was similar to that in

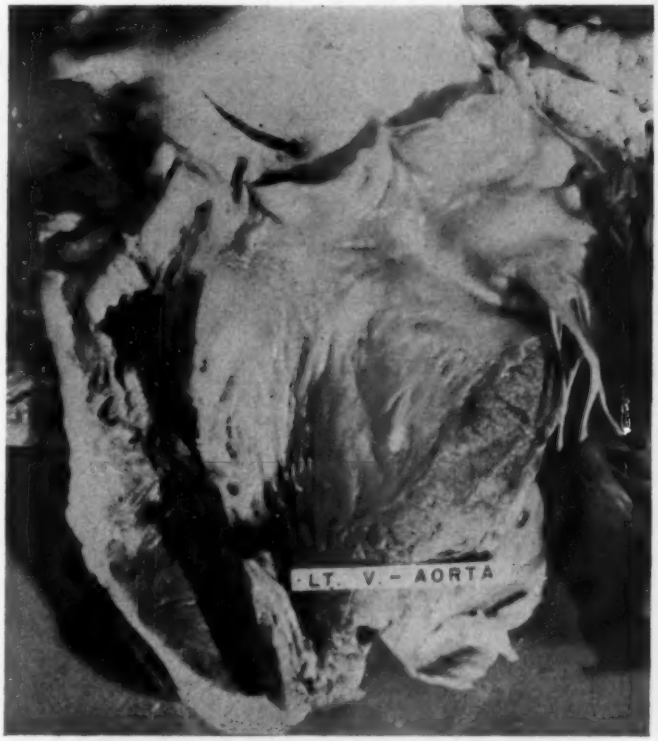

Fig. 1.—The endocardium of the left ventricle is pearl-gray in color. This change is present throughout this ventricle.

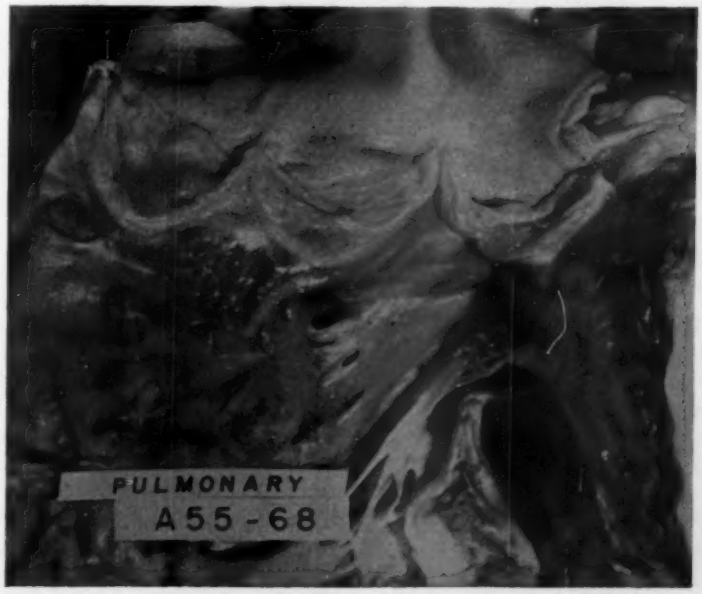

Fig. 2.—The endocardium in the right ventricle resembles that in the left, except that the degree of involvement is less.

the left (Fig. 2). A large portion of the endocardium in the left atrium (Fig. 3) and a lesser amount in the right atrium resembled that of the ventricle. In a few areas in the apex of the left ventricle this pearl-gray endocardium was slightly irregular, suggesting small wartlike nodules. The leaflets of the aortic valve were thicker than normal, but there was no fusion of the cusps. The other valves were within the range of normal.

Twenty-eight sections were taken from the heart for histologic study. They were stained by the following techniques: hematoxylin and eosin, Masson's trichrome stain, Mallory analine blue, van Gieson-Verhoeff and the periodic acid Shifft's stain. In the majority of these sections the endocardium was markedly thickened (Fig. 4); only in the right ventricle was it found to be normal (Fig. 5). This increase in thickness of the endocardium was due to a proliferation of both collagen and elastic fibers (Fig. 4). In many of the thicker areas of endocardium there was either a layer of cardiac muscle, completely surrounded by the fibroelastic tissue (Fig. 6), or a smaller

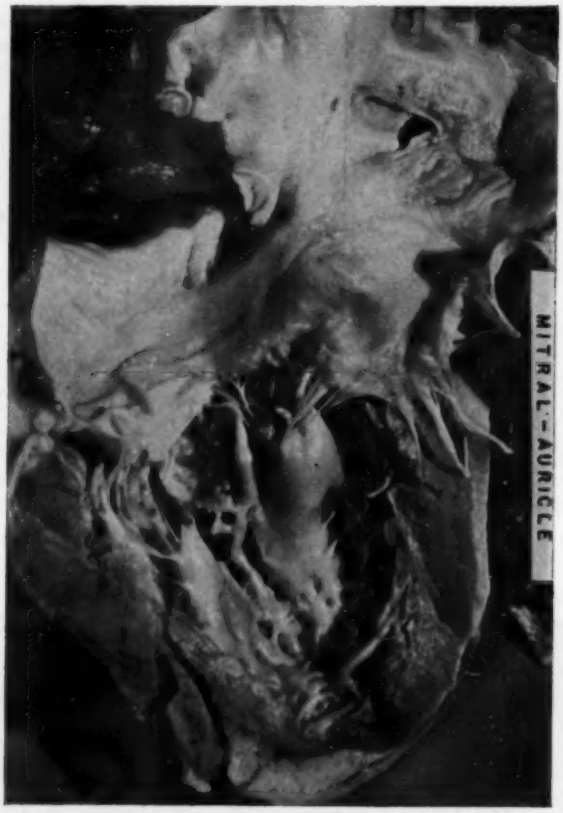

Fig. 3.—The endocardium of the left atrium is pearl-gray in color. The endocardium is less involved than it is in the left ventricle.

number of muscle cells, without striations interspersed in the endocardium, that we considered to be smooth muscle. Sometimes the fibroelastic tissue within the endocardium extended for a short distance into the myocardium. The thickened endocardium was smooth except in the apex of the left ventricle, where there were a few irregular nodules. These were formed by masses of fibroelastic tissue in which there were areas of myxomalike stroma (Fig. 7). There was a moderate amount of glycogen in this thickened area. At no point in the endocardium did we find anything to suggest an inflammatory reaction. Foci of leukemia cells were present in all portions of the heart. The myocardial fibers showed acute degenerative changes.

The lungs were edematous. The right weighed 1,200 grams and the left, 870. Some macrophages were present within the alveolae, and only a few of these showed any hemosiderinlike pigment. Few red blood cells were present in the air sacs. Focal areas of leukemia infiltration were widely distributed throughout both lungs.

The liver weighed 3,350 grams. The sinusoids were dilated and usually filled with red blood cells. Leukemic cells were conspicuous around the portal triads. Many small cholesterol stones were present in the gallbladder. No significant pathologic changes other than a few petechiae were present in the other tissue.

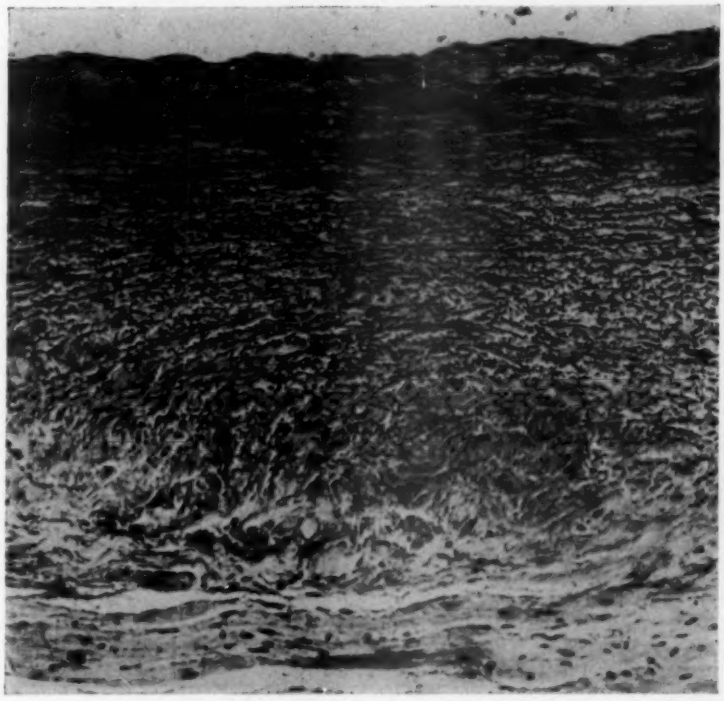

Fig. 4.—The increase in thickness of the endocardium results primarily from a proliferation of elastic and collagenous tissues. Endocardium from left ventricle. (van Gieson-Verhoeff; × 130).

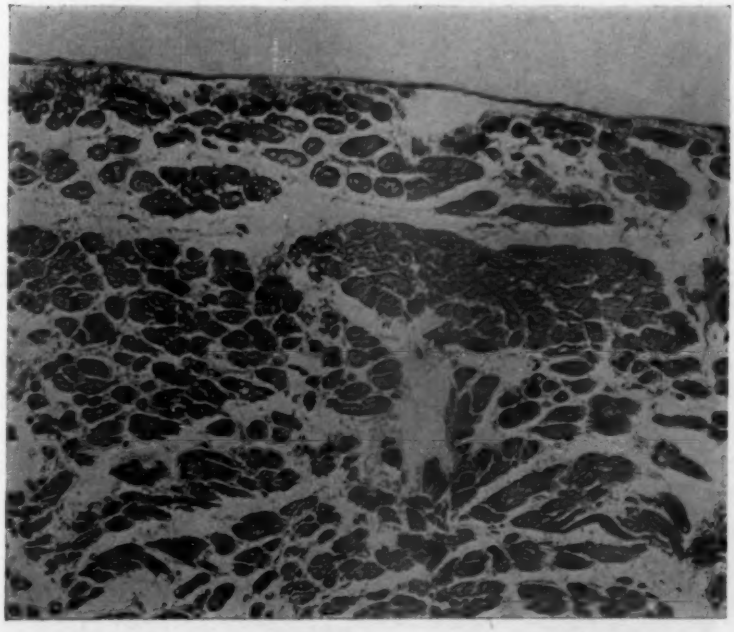

Fig. 5.—Normal endocardium in the right ventricle (hematoxylin and eosin; × 130).

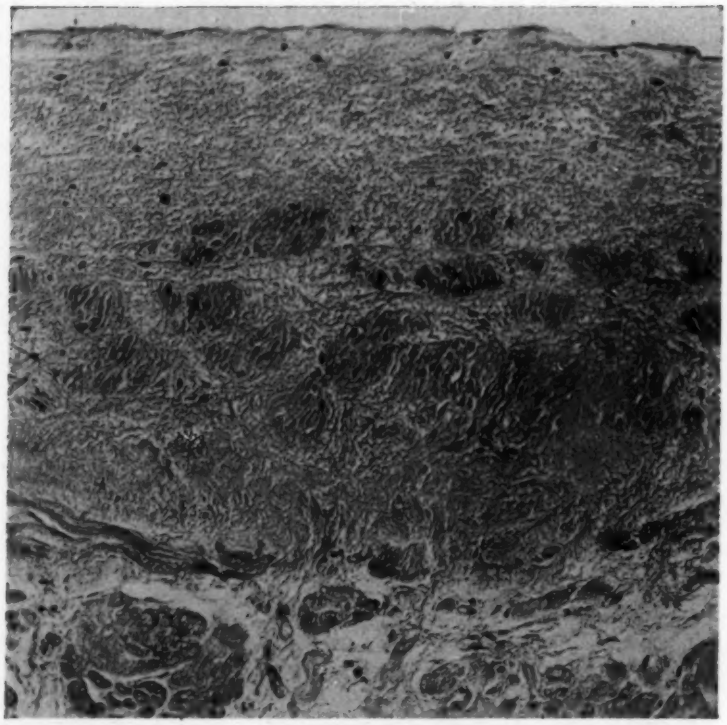

Fig. 6.—Sections from the endocardium frequently show groups of cardiac muscle fibers completely surrounded by fibroelastic tissue. These groups of muscle cells appear to be completely separated from the underlying myocardium (hematoxylin and eosin; × 130).

Fig. 7.—The endocardium in the area of the apex of the left ventricle is slightly irregular; elsewhere in the heart it is smooth. These verrucouslike areas are composed of fibroelastic tissue with some myxomalike areas. No inflammatory cells are present (van Gieson-Verhoeff; × 130).

DISCUSSION

Pototschnig,[16] in 1918, apparently was the first to suggest that endocardial thickening was the results of hyperplasia of the fibroelastic tissue. This opinion has been questioned by those who consider it secondary to an inflammatory process.[17] Our case will support the idea that fibroelastosis is congenital. The zone of cardiac muscle so frequently surrounded by fibroelastic tissue apparently can be explained only on a congenital basis. Elastic tissue is not likely to develop secondary to an inflammatory reaction,[18] a factor which will also support the congenital hypothesis. There is some evidence that heredity may exert some influence on the quantity and quality of elastic tissue.[18] The pathologic changes in this case are consistant with the opinion that fibroelastosis in the adult is congenital.

Rosahn[2] has recently suggested that the lesion within the endocardium is only one manifestation of a pathologic entity associated with generalized vascular changes. Our case did not show such a vascular lesion other than in the heart. Coarctation of the aorta may have been present in this case; if so, it was minimal. The greatly hypertrophied and dilated heart may have caused the aorta to appear smaller than normal. Cases of fibroelastosis in infants have been observed in association with coarctation of the aorta.[3,19,20]

The cardiac lesions in this case are identical with those described by Gowing[12] as typical of fibroelastosis. It is identical to the cases of fibroelastosis observed by one of us (R.H.R.) in infants and small children. This patient had this endocardial change from birth; the time at which the heart began to hypertrophy, of course, is unknown. Myocardial failure in this case no doubt was precipitated by the leukemia.

SUMMARY

The cases of fibroelastosis in adults reported from America and England are briefly summarized. Only twenty-four cases were found. The presenting clinical manifestations are those of myocardial failure. A case of fibroelastosis occurring in a white man, 38 years of age, is reported. The pathologic lesions in the heart are identical with those observed in infants. This process in the adult is considered congenital. The histologic findings in support of this opinion are the absence of any inflammatory reaction, and the presence of elastic tissue, and a thin band of cardiac muscle in the thickened endocardium. All cases of fibroelastosis in adults should be carefully studied in an attempt to better understand this cardiac lesion.

SUMMARIO IN INTERLINGUA

Es presentate un breve summario del casos de fibroelastosis reportate ab America e Anglaterra. Solmente vinti-quatro casos esseva trovate. Le manifestationes clinic responsabile pro le presentation del patientes es manifestationes de disfallimento myocardial. Es reportate un caso de fibroelastosis in un masculo blanc de 38 annos. Le lesiones pathologic in le corde es identic con le lesiones observate in infantes. Iste processo in adultos es considerate como congenite. Le constatationes histologic que supporta iste conception es le ab-

sentia de reactiones inflammatori e le presentia de histos elastic e de un tenue banda de musculo cardiac in le spissificate endocardio. Omne casos de fibroelastosis in adultos deberea esser studiate cautemente pro adder a nostre comprension de iste lesion cardiac.

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Review

THE MANAGEMENT OF COR PULMONALE IN CHRONIC PULMONARY DISEASE, WITH PARTICULAR REFERENCE TO THE ASSOCIATED DISTURBANCES IN THE PULMONARY CIRCULATION

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INTRODUCTION

DIFFUSE pulmonary disease may impose a considerable burden upon the heart. The designation "cor pulmonale" is generally applied to a heart which manifests dilatation, hypertrophy, or failure secondary to intrinsic disease of the lungs. The cardiac enlargement and failure are confined largely, if not wholly, to the right heart; indeed, in the occasional instances of concomitant left ventricular enlargement or failure, it may be assumed that there is independent and unrelated disease of the left heart. This definition of cor pulmonale also implicitly excludes hypertrophy, dilatation, or failure of the right ventricle secondary to disease of the left heart, e.g., mitral stenosis.

The common denominator in the evolution of cor pulmonale, since there is no intrinsic underlying heart disease, is an increase in the work of the right heart. More specifically, the increased work is generally due to an increase in pressure-work, manifested by pulmonary hypertension. In some instances, especially in chronic pulmonary emphysema, the augmented pressure-work may be associated with an increase in volume-work, due to an increase in cardiac output.

Granting its multiple physiologic causes, one should perhaps emphasize again that cor pulmonale is still defined in anatomic terms—a dilatation or hypertrophy (or both) of the right heart of significant extent, secondary to pulmonary disease. Mere pulmonary hypertension does not constitute cor pulmonale, any more than systemic arterial hypertension defines left ventricular heart disease.

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On the other hand, cor pulmonale includes both the compensated and the uncompensated states. A significant enlargement in right ventricular outline by x-ray, together with other evidence of right heart hypertrophy, establishes a diagnosis of cor pulmonale even though the heart and circulation are physiologically entirely compensated.

INCIDENCE

Right heart strain and failure are generally late developments in the natural history of lung disease. The majority of chronic pulmonary diseases pursue their course without manifesting circulatory impairment. Nonetheless, because of the prevalence of diffuse lung disease, cor pulmonable is not an uncommon type of heart disease. It has been extensively investigated as a complication of chronic pulmonary emphysema, particularly obstructive emphysema secondary to chronic bronchitis[3,30]; although it also occurs in patients with either asthmatic or bullous emphysema,[4,25,51] fewer instances of the latter types of emphysema are available for study.

Cor pulmonale and pneumonia are common terminal events in advanced silicosis or silicotuberculosis.[27] Cor pulmonale also occurs with other forms of severe destructive or infiltrative fibrotic disease, such as fibrotic tuberculosis. In some patients with extensive pulmonary disease, right heart strain and failure may be precipitated, or aggravated, by surgical procedures which entail excision or collapse of functioning lung segments.

Cor pulmonale is also recognized as a common late event following extensive impairment to diffusion of oxygen, as occurs in alveolar-capillary block due to fibrosis or granuloma[1,2]; it is a dreaded complication of severe kyphoscoliosis, of chronic, multiple pulmonary embolization,[40] and of the ill-defined, but apparently real, category of primary pulmonary hypertension.[12,19,26]

When cor pulmonale does occur in association with these various types of lung diseases, the pattern of physiologic derangements, and therefore of clinical manifestations, may be widely disparate.[9,14,15,17,36,37,48,49] The characteristic alterations in physiologic mechanisms, as well as in the clinical patterns or syndromes, will be described in the succeeding pages.

PHYSIOLOGY OF PULMONARY HYPERTENSION AND DEVELOPMENT OF COR PULMONALE

In the normal individual, the pulmonary circulation is a highly distensible, capacious low pressure system. A cardiac output of 5 to 6 liters per minute at rest is accommodated with pulmonary arterial pressures of 20 to 28 mm. Hg in systole, and 8 to 12 mm. Hg in diastole; increases up to three times this blood flow, as occurs during moderate exercise, are associated with a rise in pulmonary arterial pressures of only a few mm. Hg.[28,45]

As implied in the preceding paragraph, restriction and decreased distensibility of the pulmonary vascular bed, leading to increased resistance to blood flow, is a much more important cause of pulmonary hypertension than is increase in blood flow.[14,15,20] Anatomic restriction of the vascular bed may be accomplished by a variety of different pathologic alterations.[12,32,35] Thus, a critical reduction in the extent of the pulmonary vascular bed can occur from diminution

in total lung tissue, from extensive decrease in the pulmonary capillary bed,[30] from arteriosclerotic narrowing and medial hypertrophy, with thickening and constriction of smaller pulmonary arteries and arterioles, and from multiple pulmonary emboli,[40] or thrombosis.[13] In endemic areas, schistosomiasis is a prominent cause of cor pulmonale. Rarely, obstruction of the pulmonary veins, incident to displacement and kinking, or to mediastinitis, may cause pulmonary hypertension by augmenting resistance to blood flow while concomitantly increasing pulmonary blood volume and thereby decreasing pulmonary vascular distensibility. Extravascular compresssion and loss of elasticity from surrounding parenchymal disease are additional factors which may increase pulmonary vascular resistance.[32,35]

It is important to stress that the normal pulmonary vascular bed provides a large reserve for ordinary physical activity: normal pressure-flow relations can continue at rest with as little as one third of normal functioning lung. Indeed, even patients who have had a pneumonectomy can accommodate a two- or threefold increment in pulmonary blood flow with only a minimal increase in pulmonary artery pressures, as long as the remaining lung is free of fibrosis, emphysema, or pulmonary vascular change.[16]

In patients with obstructive disease of the bronchi, generally associated with progressive obliteration of alveolar-capillary surface by inflammation, atrophy, and scarring, the normal balance between alveolar ventilation and capillary perfusion may become disrupted to a degree sufficient to cause systemic arterial hypoxemia. Systemic arterial hypoxemia elicits, in turn, a train of events including polycythemia and hypervolemia, augmented pulmonary blood flow, and possibly pulmonary vasoconstriction,[22,24,33,38] all contributing to the increase in pulmonary hypertension.[15,20,27] With respect to therapy, it is particularly important to note that, in the patient with cor pulmonale secondary to chronic obstructive pulmonary emphysema, the total effects of the potentially reversible chemical stimulus of hypoxemia probably play a greater role in eliciting pulmonary hypertension than do the irreversible anatomic alterations of the vascular bed.

In the group of patients with chronic obstructive emphysema, with markedly defective aeration of alveolar spaces, inadequate "pulmonary emptying," and progressive disruption of normal alveolar ventilation-perfusion relations, arterial hypoxemia is eventually accompanied by some degree of carbon dioxide retention. Chronic carbon dioxide retention with elevated carbon dioxide tensions in blood and tissues has two further effects: a retention of bicarbonate by the kidney,[11,18] and a depression of the sensitivity of the respiratory center to the carbon dioxide stimulus[23]: both of these effects, in turn, promote further carbon dioxide retention.

It is particularly in this group with carbon dioxide retention, that severe chronic congestive heart failure occurs; the congestive state is characteristically associated with severe hypoxemia, hypercapnea, hypervolemia, polycythemia, and increased cardiac output (Ayerza Syndrome).[3,7] It is not known to what extent the chronic increase in the carbon dioxide levels in blood and tissues contributes to the cardiac burden.

With respect to the increased work of the right heart, a final word may be added concerning the marked respiratory variations in pulmonary artery blood pressure which are observed in blood pressure records obtained from patients with chronic lung disease.[8,31] Although these blood pressure variations are undoubtedly associated with considerable variations in pulmonary blood volume and flow, they apparently are not an important element in the evolution of cor pulmonale.

THE HEART IN CHRONIC COR PULMONALE

In the resting subject, a mean inflow pressure of a few mm. Hg in each atrium suffices to fill each ventricle of the heart to a volume of approximately 150 c.c.; during each systole, about half of this volume is ejected. The output of the left heart is very slightly (perhaps 1 to 2 c.c. per beat) greater than the right, because a part of the bronchial artery blood flow returns directly to the left heart via the pulmonary veins, without traversing the right heart.[34] During exercise, the normal heart increases its stroke output by more complete emptying of the residual volume, and is actually smaller than the resting heart.

The normal heart is also able to enlarge and to accommodate greater diastolic volumes, with imperceptible change in pressures or output; this type of adaptation occurs following assumption of the supine position or in response to an increase in blood volume. These are normal adjustments due to alterations in cardiac "tone," and, therefore, need not be considered as contradictions of the Starling principle.[42]

An interesting adaptation that has many analogies with chronic pulmonary heart disease is that encountered in permanent residents at high altitudes. These individuals have marked polycythemia, increased blood volume, increased chest and lung volumes, and increased cardiac output. Pulmonary artery pressures either remain within normal limits or are somewhat elevated, and the heart, although enlarged with right ventricular hypertrophy, fills and empties without evidence of failure.[46]

In considering the development of heart disease due to lung disease, it should be emphasized again that moderate, or even considerable restriction of pulmonary function—either restrictive, obstructive, or alveolar-respiratory—may exist with little or no increase in pulmonary arterial pressures, and no evidence of cor pulmonale.

As pulmonary vascular resistance increases due to progression of parenchymal or vascular disease, pulmonary hypertension becomes manifest during periods of increased pulmonary blood flow, e.g., exercise.[28,45] In time, pulmonary hypertension may even be present at rest. However, although the existence of pulmonary hypertension may be suspected, it cannot be proved clinically. Furthermore, evidences of cor pulmonale generally do not appear until pulmonary artery pressure exceeds twice normal.[29] In a patient with chronic lung disease, cor pulmonale is suggested by the presence, on x-ray, of an enlarged right ventricle and a prominent, dilated pulmonary artery, as well as electrocardiographic evidence of marked right axis shift, right ventricular hypertrophy, or incomplete right bundle branch block. An accentuated second pulmonic sound, often associated with pulmonary hypertension, is not pathognomonic of this condition.

These considerations suggest that the earliest evidence of incipient cor pulmonale can be obtained only by direct measurement of pulmonary artery pressure, i.e., by cardiac catheterization.

In this early clinical stage, cardiac catheterization has demonstrated that the heart maintains a normal output at rest, with a normal increment in flow during exercise. A first evidence of right heart "strain" during exercise is an increase in right ventricular end-diastolic (filling) pressure up to 7 to 10 mm. Hg, a reflection of the beginning of inadequate ventricular emptying.

With further increase in pulmonary vascular resistance, especially if there is concomitant hypoxemia and hypervolemia, the signs become more overt, and failure of right ventricular emptying occurs, with cardiac dilatation, increased venous pressure, and peripheral edema. At this stage, pulmonary artery pressures are high, reaching systolic pressure levels of 70 to 90 mm. Hg and diastolic pressures of 30 to 50 mm. Hg.

Clinically, the onset of right heart failure may be insidious, with gradually increasing edema of ankles and legs over days or weeks; on the other hand, right heart failure may appear suddenly, especially during an acute respiratory infection and acute pulmonary insufficiency. The clinical identification of a primary pulmonary etiology for the heart failure is supported when arterial blood analyses show that oxyhemoglobin saturation is below 85 per cent, when polycythemia is marked and when the content and partial pressure of carbon dioxide are increased. When, however, pulmonary insufficiency and dyspnea are present without disturbances in blood gas composition, the differentiation of cor pulmonale from combined right and left heart failure may be difficult. In this case, urgent orthopnea, as elicited by the appearance of both dyspnea and basal pulmonary râles, after a few minutes in the supine position, may serve as a useful index of left ventricular failure.

Gallop rhythm is common in cor pulmonale, but permanent arrhythmias, such as atrial flutter or fibrillation, are rare. The occurrence of hydrothorax is uncommon in cor pulmonale, even after the advent of frank congestive failure.

The congestive state in the right heart failure of cor pulmonale may differ dynamically from that observed in the heart failure of intrinsic heart disease by virtue of a tendency toward increase, rather than decrease in cardiac output.[15,17,36,48] This tendency toward augmented resting cardiac output, in the face of severe right heart failure, reaches its peak in the types of cor pulmonale with "Ayerza's Syndrome," i.e., congestive state in association with hypoxemia and polycythemia[7]; it may be less marked, or even absent, late in the course of "Ayerza's Syndrome" as well as throughout the entire development of other forms of cor pulmonale. Although the increased cardiac output may be in part stimulated by hypoxemia, it is to a greater extent induced by the overfilling of the heart and vascular bed by the excessive hypervolemia. It therefore emerges as a direct "Starling" effect, similar to that produced in the normal circulation by large intravenous infusions.[42] Correspondingly, a reduction in blood volume in patients with the "Ayerza Syndrome," is regularly followed by a fall in cardiac output toward normal.

CLINICAL FORMS OF COR PULMONALE AND THEIR TREATMENT

The many forms of chronic pulmonary disease that have cor pulmonale as an important late complication may, for the sake of consideration, be divided into three groups: (a) A group in which the major factor is anatomic narrowing or reduction of the pulmonary vascular bed; (b) The group of diffusion insufficiency or "alveolar-capillary block," characterized by impaired gas exchange between alveolar gas and pulmonary capillary blood; and (c) The group of "high output failure," composed chiefly of cases of chronic diffuse obstructive emphysema with maximal disturbance of ventilation-perfusion relationships.

A. *Critically Diminished Pulmonary Vascular Bed.*—Critical anatomic reduction in pulmonary substance with corresponding over-all diminution in pulmonary vascular bed occurs in: (1) long-standing pulmonary tuberculosis in the fibrotic stage, with shrunken lobes, regional emphysema, chronic pleurisy, or fibrothorax, sometimes aggravated by excisional or collapse surgery; (2) bullous or atrophic emphysema with much loss of lung substance; (3) other forms of extensive conglomerate fibrosis, as seen in advanced silicosis; and (4) severe kyphoscoliosis.

These patients continue for long periods, usually many years, with symptoms of progressing ventilatory insufficiency, chiefly dyspnea. Eventually, often at the stage when hypoxia has become more marked, ankle swelling, with or without other evidences of congestive failure, begins. The next stage is often that in which an intercurrent respiratory infection precipitates an acute episode of right heart failure. At such times, there is usually a marked increase in arterial hypoxia, not infrequently accompanied by an acute rise in blood carbon dioxide. Congestive failure develops rapidly, there is liver enlargement, more or less peripheral edema, and an increase in blood volume. There is often some polycythemia, with hematocrit a better index than hemoglobin.

The patient may persist in this stage, going in and out of heart failure with each respiratory infection for months or years. Ultimately, if the patient survives the acute episode, there evolves the later stage of permanent extreme hypoxia, intermittent carbon dioxide retention, and chronic congestive failure.

An important physiologic characteristic of this group is the normal or low cardiac output in the compensated stage of cor pulmonale, with a further decrease as heart failure supervenes and becomes chronic.[27]

As a somewhat similar subgroup may be mentioned those cases in which pulmonary arteriosclerosis or intrinsic disease of the pulmonary vascular bed constitutes a major cardiac burden. To a considerable extent, this group merges with that just described, since long-standing pulmonary hypertension from any cause tends to aggravate itself by the production of pulmonary medial hypertrophy with narrowed lumens. On the other hand, two clinical entities have been identified in which cor pulmonale evolves following primary vascular rather than primary parenchymal disease: "primary" pulmonary hypertension, and multiple pulmonary embolization. In these patients, cor pulmonale and right heart failure evolve gradually; in the final stages of the disease, and even at autopsy, the distinction between "primary" pulmonary hypertension and healed pulmonary emboli may be difficult to establish.[40]

The treatment of this whole group is tempered by the awareness that the increased pulmonary vascular resistance is more or less fixed and irreversible, so that only partial restoration of cardiac function can be anticipated. Although vasoconstriction has been suggested as a factor contributing to increased pulmonary vascular resistance, particularly in instances of "primary pulmonary hypertension," the analysis of the effects of vasodilator drugs, e.g., Priscoline,[19] in specifically relaxing pulmonary vessels, is complicated by concomitant hypotension in the systemic circulation.

As with all cor pulmonale, first attention should be directed to treatment of the pulmonary disease: available agents include antibiotic therapy, bronchodilator drugs, antitussive agents, etc. In most patients of this group, in the early stages oxygen therapy can be used freely, in whatever concentration needed, without the risk of carbon dioxide retention.[5,6] In patients with far advanced pulmonary disease and severe pulmonary insufficiency, carbon dioxide retention may occur; in such patients, the administration of greatly enriched oxygen mixtures, greater than 60 to 70 per cent, entails the hazard of further carbon dioxide retention.[3]

Respirators will often be helpful in the bullous emphysema cases. Although they may be of some help in relieving the dyspnea of other types of disease in this group, they generally prove less effective.

Cardiac therapy includes, of course, digitalization, low salt regimen, and diuretics. Phlebotomy of 500 c.c. is of value when the congestive state is definitely established, with enlarged liver, etc., and when the hematocrit is elevated.

In the rather uncommon, late development of persistently elevated carbon dioxide, diamox may be used, in doses of 250 mg. or 500 mg. daily.[23]

B. *Impaired Alveolar-Capillary Diffusion of Oxygen.*—The group of diffusion insufficiency or alveolar-capillary block[1,2] includes: (1) the various granulomatoses of the lung, such as sarcoidosis, berylliosis, and the "nonspecific" granulomatoses; (2) scleroderma of the lung; (3) the various interstitial or alveolar-septal fibrosis such as "nonspecific" infections, pulmonary asbestosis, or the special progressive form known as the "Hamman-Rich Syndrome"; (4) the rare pulmonary adenomatosis, or "alveolar-cell" carcinoma.

Physiologically, the essential characteristics are: marked hyperpnea, arterial hypoxemia on exercise (later, also at rest); carbon dioxide levels slightly low or normal; often an increased oxygen consumption; and cardiac output somewhat above normal in early stages, becoming low, or even very low, when cor pulmonale with failure has developed. This complication, except for the patients with "Hamman-Rich Syndrome," generally occurs quite late in the course of the disease.

As regards treatment, most of the general principles previously stated can be applied. In advanced cases, oxygen therapy usually has to be given continuously and in high (approaching 100 per cent) concentrations.[43] An important special measure in the granulomatoses is steroid therapy.[50] This is sometimes dramatically successful, restoring patients to nearly normal physical activity. In other cases, especially those of long standing, it may be without effect, or even harmful.

C. *Inhomogeneity of Alveolar Ventilation and Perfusion.*—Polycythemic obstructive emphysema, or the "Ayerza Syndrome," or the "black cardiac" as described by South American investigators,[3,7] is, in its fully developed form, relatively uncommon. It is, however, a clearly defined condition, both physiologically and clinically. The patient's history is usually one of long-standing asthma and obstructive dyspnea. On physical examination, and by x-ray, the evidences of alveolar distention may be rather mild, certainly slight when compared to that seen in severe bullous emphysema. The spirogram suggests severe obstruction to expiration and residual volumes are large. The outstanding physiologic disturbance, however, is alveolar-respiratory, i.e., an excessively poor aeration of perfused alveoli, resulting in profound arterial hypoxemia and carbon dioxide retention. The impaired gas exchange stems from a virtual disruption of normal alveolar ventilation-perfusion relationships. With this hypoxemia and hypercapnia is associated the overproduction of red blood cells, polycythemia, and increased blood volume, this increase being due wholly to increase in red cell mass. Despite the extensive pathologic changes in pulmonary parenchyma, the evolution of pulmonary hypertension is apparently almost wholly due to the combined effects of (a) the hypoxic stimulus, (b) the increased pulmonary vascular congestion, (c) the increased blood viscosity, and (d) the increased cardiac output.

The resulting cardiodynamic picture in a far-advanced case of this group with cor pulmonale, heart failure, and the congestive state is of the "high output" type. A typical series of measurements might be: arterial oxyhemoglobin saturation 60 per cent, arterial blood carbon dioxide tension 65 mm. Hg, pulmonary arterial pressure 70/40 mm. Hg, hematocrit 65 per cent, blood volume 8000 c.c. (50 per cent above normal), and cardiac output 11 liters per minute (twice normal).

The compensatory aspect of the polycythemia in these cases, as argued by Taquini,[48] is, in our experience, wholly overshadowed by the other unfavorable effects of the polycythemic state.[41]

As the causes of cor pulmonale in these cases, in contradistinction to those previously described, are largely chemical and dynamic, and not anatomically fixed, treatment is often remarkably successful in bringing the circulation back to normal. Pulmonary function should be treated according to the general principles already stated. Restlessness and even belligerence may reflect carbon dioxide retention; particular care must be exerted to avoid the use of sedatives which may depress the respiratory center, e.g. morphine, since their use entails the hazard of further increasing carbon dioxide retention and promoting narcosis. Special effort should be directed toward opening and clearing the air passages. Acute airway obstruction may require suction. The bronchodilator aerosols, 5 to 10 drops vaporized from an oxygen tank or motor blower, and inhaled for ten minutes systematically three or four times daily, should be a basic routine. After each treatment, the patient should be encouraged to cough and raise sputum. Steroids, in small doses, particularly prednisone, have been of benefit in some patients with refractory bronchospasm. As airway obstruction and hypoxemia are relieved, the work of breathing decreases and dyspnea generally

becomes less troublesome. Oxygen therapy is usually indicated, but must be given cautiously to avoid further carbon dioxide retention and carbon dioxide narcosis[3]; oxygen administration, through a nasal catheter, at 3 to 5 liters per minute may be sufficient to maintain virtually normal arterial oxyhemoglobin saturations.

In the more severe degrees of hypoxemia and hypercapnea, with depressed respiratory center, mechanical aids to respiration will be needed.[39,44] The simplest are the various forms of intermittent positive pressure respirators, the Bennett, the Emerson, the Mine-Safety Appliance, and similar forms. Some of these require the patient's own spontaneous inspiratory effort to start the inspiratory cycle. The administration of high oxygen to such patients may deprive the patient of the low-oxygen respiratory stimulus and result in sudden apnea; these hypercapneic patients require either an apparatus that cycles automatically or else the substitution of a compressed air tank for the oxygen tank.

When treatment is begun, these types of artificial respiration should be used for the greater part of the day; the optimal duration and the effectiveness of treatment may be gauged after temporarily discontinuing the respirator from arterial blood analyses for gaseous composition and hydrogen ion concentration. In time, as the other therapeutic measures take effect, and as hypoxemia and hypercapnea are somewhat relieved, briefer periods of respirator treatment will be required, e.g., periods of one-half to one hour, at regular intervals, throughout the day.

In the most extreme situations, the tank respirator of the Drinker type may be required, generally for a few days, but sometimes as long as for two to three weeks.[10] In this situation, the ancillary measures are continued and pure oxygen and even sedatives may be administered since breathing is automatically regulated. The use of the tank respirator requires expert nursing care; withdrawal from the respirator is based on evidences of clinical improvement coupled with restoration toward normal of the arterial blood gaseous composition.

After recovery from heart failure, less drastic forms of respiratory aid, including breathing exercises, head-down position, etc., may be helpful, or the patient may continue indefinitely with a program of mechanical respirator, two or three times a day, plus bronchodilator.

Treatment of the cor pulmonale itself will be governed by the principles already stated for other forms: digitalization, low sodium regimen, mercurial diuretics. As in other forms of heart failure, the treatment of the congestive state includes a period of bed rest; however, it must be stressed that prolonged inactivity and quiet breathing promotes stagnation of bronchial secretions. In these patients, the ventilatory insufficiency which, in turn, contributes to heart failure may improve considerably following the resumption of mild activity and the deliberate increase in respiratory movements.

In addition to the general cardiotonic program, active measures to decrease blood volume assume a very important role in decreasing the cardiac burden. Often several 500 c.c. phlebotomies will be needed within a two or three week period to bring hematocrit and blood volume back to normal, as well as repeated phlebotomies at monthly or bimonthly intervals to prevent return of hyper-

volemia. Diamox is also useful as a continuous medication, not only to help prevent return of carbon dioxide retention and chronic elevation of blood bicarbonate, but also to promote, albeit weakly, the renal excretion of sodium.[21,23]

The effects of vigorous therapy upon a patient with this syndrome in the stage of severe failure are often most dramatic: within two weeks to a month's time, arterial oxygen saturation will be restored to a 91 or 93 per cent level, carbon dioxide levels become normal, and blood volume, hematocrit, cardiac output, and even pulmonary arterial pressures are restored to completely normal values.

By careful management, these patients can be carried fairly successfully for five- to ten-year periods, though eventually they become cardiopulmonary cripples, wholly dependent on respiratory aids.

COR PULMONALE IN ASSOCIATION WITH INTRINSIC HEART DISEASE AND LEFT VENTRICULAR FAILURE

It seems clear that, in the older patients with cor pulmonale, there may well be a contribution of left ventricular failure due to independent left heart disease. The presence of intrinsic left ventricular disease may be suggested by orthopnea, and supported by x-ray and electrocardiographic evidence of left ventricular hypertrophy. Nonetheless, in individual instances, particularly in the acute congestive states, the element of left ventricular failure may be difficult to establish; in this respect, it is worthy of note that physiologic identification of the predominant ventricular failure may be facilitated by measurements of pulmonary artery pressure and flow during right heart catheterization. This distinction is based on the change in pulmonary artery pressure which follows acute digitalization, i.e., a fall in pressure in patients with predominant left ventricular failure as opposed to a rise in patients with predominant right ventricular failure due to cor pulmonale.[20] Finally, from the point of view of therapy, the identification of a component of left ventricular failure in a patient with cor pulmonale and right heart failure is relatively unimportant, since both types of failure respond well to cardiotonic programs which include salt restriction, digitalis, and diuretics, as well as to the general measures which are entailed in the adequate treatment of cor pulmonale.

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Announcements

The UNITED STATES PUBLIC HEALTH SERVICE has announced a new procedure to expedite the processing of RESEARCH GRANT APPLICATIONS for those requests which do not exceed $2000 plus indirect costs, and which do not ask support for more than one year. Such applications will be accepted and processed on receipt and are not, therefore, subject to the usual deadlines for submission prior to review.

Council recommendations can be expected on these applications within one to four months from the time of submission. These procedures do not apply for requests for supplements to existing grants.

Address all applications, as well as requests for forms or additional information to the Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION FOR GRADUATE PHYSICIANS will be given at the Michael Reese Hospital by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., August 20 through September 1.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Margaret Stern, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

Book Reviews

HIGH BLOOD PRESSURE. By G. W. Pickering, New York, 1955, Grune & Stratton, Inc., 547 pages

In this monograph the author approaches the problem of high blood pressure with the concept that "hypertension" should not be considered a sharply delineated pathologic entity, but that regulation of the blood pressure is a function which, under the influence of certain factors, ("stress," although the author does not entirely subscribe to the stress concept of Selye) may deviate from the physiologic and cause changes which may interfere with the patient's health and life expectancy. With other words, the term "high blood pressure" occurs in a number of different clinical conditions which gradually merge with the normal. The author believes that many erroneous beliefs and futile therapeutic approaches have resulted because it was believed that hypertension was a "disease" and that if the "cause" of it could be discovered the "cure" would be indicated.

Thus in changing the light in which this important condition should be studied, the author gives expression to a change which appears to be developing in many fields of medicine, and for this reason alone the book represents a real addition to medical literature.

In addition, it submits to critical analysis a wealth of data pertinent to the regulation of the blood pressure, and the failure of this regulation. The author draws from his own rich experience and from the literature the important contributions of the past, so the reader is left with a fairly clear distinction between what we know and what we only thought we knew about the blood pressure and hypertension. He has even had access to much material which was not yet published at the time of the writing of the book.

Besides discussion of the blood pressure and the conditions which surround the problem of essential hypertension, there are also brief reviews of conditions in which hypertension is an important albeit secondary factor, such as pyelonephritis, polyarteritis nodosa, and Cushing's disease. Chapter 23 is devoted to an important discussion of pregnancy and hypertension.

J. J.

CARDIAC DIAGNOSIS—A PHYSIOLOGIC APPROACH. By Robert F. Rushmer, M.D., Philadelphia, 1955, W. B. Saunders Company, 447 pages with illustrations. Price $11.50.

This is an interesting and stimulating book. As the author points out, a book of this sort represents only a small sample of facts and concepts from the vast store of material on the subject. The content is much influenced by the research interests of Dr. Rushmer and his group. These are sorted out into an exposition of so-called vertical teaching, incorporating anatomy, physiology, pathology, and clinical medicine as related to the heart. Many interesting and somewhat unusual concepts are presented and the book is extensively illustrated by excellent charts and diagrams. Because of the nature of the volume there are certain omissions. For instance, there is no discussion of pericardial function nor of pericardial disease. The many clinical situations are presented in a very brief fashion so that it is perhaps unfortunate that the book has the title of "Cardiac Diagnosis." It is in reality a discussion of pathophysiologic concepts that underline cardiac diagnosis and it is not directed primarily at the use by the clinician in making clinical diagnoses, but rather in their understanding. In no way, therefore, is it a substitute for one of the standard text books on heart disease. It offers an interesting adjunct of stimulating reading, strongest where Dr. Rushmer has major interests, but all in all, a recommended book.

J. V. W.

CARDIOVASCULAR SURGERY. By Gerald H. Pratt, Philadelphia, 1954, Lea & Febiger.

In the preface to his *Cardiovascular Surgery* the author states his purpose "to bring to surgeons, internists, and students a summary of accepted or acceptable treatment for cardiovascular lesions," and later "to bring the subject matter up to date." Undismayed by the vast territories which this surgery now encompasses, he has ventured to add several chapters which others would be glad to omit. For example, the first chapter includes the index numbers of the vascular portions of *The Standard Nomenclature of Disease* and again near the book's end is a section devoted to "Radioactive Isotopes and Atomic Energy."

To cover all this and cardiovascular surgery, too, Dr. Pratt elects the encyclopedic approach. Very well classified and nicely indexed, any given disease or lesion is easily found. In general, diagnostic procedures are well covered, but in discussing many particular lesions, diagnosis and particularly differential diagnosis are deficient.

Almost all of the recognized treatments are given, but there is very little to aid the uninitiated in selecting the method of choice. This manner of impersonally generalizing his subject matter is not helped by the roughly 1,600 references which (while no doubt making the book "authoritative") do little to crystallize one's thoughts.

In contrast to the thirty pages in which congenital heart disease is discussed, the author's long interest in peripheral vascular lesions leads him to devote some 600 pages to these latter subjects. It is clearly in this section of the book that its greatest value lies. The section on hypertension is especially well done and here the criticisms mentioned above are less evident.

R. E. G.